



# The Sri Lanka Prescriber

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# The Sri Lanka Prescriber

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## Correction

### Legend of June 2008 cover picture



*The legend for the cover picture of The Sri Lanka Prescriber, June 2008 should have been*

### Pharmacy today and tomorrow

Pharmacy has come through many revolutions, developed new techniques, discarded older ways. Its professional stature will continue to grow as its tradition of service is passed on from preceptor to apprentice, teacher to student, father to son.

One of a series: *A History of Pharmacy in Pictures*, presented by Parke, Davis & Company.

George A. Bender, Director © 1957 Robert A. Thom, Artist

### Cover picture

#### First apothecary shop (754 A. D.)

Arabs separated the arts of apothecary and physician; established first privately owned drug shops in Bagdad in the eighth century; carried pharmaceutical science back to Western Europe following Moslem conquests.

One of a series: *A History of Pharmacy in Pictures*, presented by Parke, Davis & Company.

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# Management of conjunctivitis

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Inflammation of the conjunctiva (conjunctivitis) is one of the commonest eye diseases worldwide.

The conjunctiva consists of a stratified columnar epithelium studded with goblet cells on the surface and a stroma of loose vascular supporting tissue. It covers the inner aspect of the lids and the anterior part of the sclera.

The symptoms of conjunctivitis occur due to inflammation of different components of this tissue. Hyperaemia, irritation, tearing, and sticky eyes are common. The onset, nature and duration of each of the signs and symptoms should be considered in the differential diagnosis of conjunctival inflammation (1). The ocular, medical and medication history as well as specific environmental and work-related exposures are pertinent.

Based on the duration, acute conjunctivitis by definition lasts less than four weeks, and chronic conjunctivitis is a persistence of symptoms for more than four weeks (2).

Aetiologically conjunctivitis is mainly of two types; infective and non-infective (table).

**Table. Types of conjunctivitis**

---

|               |  |
|---------------|--|
| Infective     | Viral eg. Adenovirus, Herpesvirus<br>Bacterial eg. <i>Staphylococcus</i> ,<br><i>Streptococcus</i> , <i>Neisseria</i> , <i>Haemophilus</i><br><i>Chlamydia</i><br>Fungal eg. <i>Candida</i> , <i>Rhinosporidium</i><br>Parasitic eg. <i>Ascaris</i> , <i>Pthirus pubis</i> |
| Non-infective | Chemical eg. acid, alkali, preservatives<br>of topical medications<br>Immunological eg. allergic, vernal, atopic,<br>Associated with dry eye, contact lenses,<br>thyroid disease, sarcoidosis,<br>Idiopathic   |

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## Unilateral or bilateral

Bilateral red eye occurring simultaneously would be more in favour of an allergic aetiology, secondary to exposure to an environment allergen or to a medication used on both eyes. In contrast, infective conjunctivitis usually starts in one eye and spreads to the other a few days later.

## Discharge

The type of ocular discharge may be helpful in differentiating the underlying cause. Commonly a serous (watery) discharge occurs in viral or allergic conditions and a muco-purulent or purulent discharge is more suggestive of a bacterial cause. A mucoid (stringy or ropy) discharge is highly suggestive of an allergy or dry eyes.

## Itching

Itching is the hallmark of allergic conjunctivitis. Lid scratching, with tearing and redness occurring intermittently, is seen in blepharitis.

## Conjunctival injection

Conjunctival injection is usually more in the forniceal than in the bulbar conjunctiva in infective conjunctivitis but in inflammation due to allergy or dry eye, bulbar conjunctival injection is commonly seen.

Subconjunctival haemorrhages, a rather alarming sign to the patient, occurs in viral (adenovirus) and bacterial (*Streptococcus pneumoniae* and *Haemophilus aegypti*) infections.

## Follicles and papillae

Follicles are sub-epithelial foci of hyperplastic lymphoid tissue appearing as small grains of rice in the fornices, commonly seen in viral and chlamydial infections, and following hypersensitivity to topical medication.

Papillae are hyperplastic conjunctival epithelium thrown into projections with central vessels, commonly occurring in the upper palpebral conjunctiva (best seen when the upper lid is everted). Although non-specific, their occurrence is commonly associated with chronic blepharitis, allergic and bacterial infections, and following contact lens wear.

## Lymphadenopathy

Pre-auricular and submandibular lymphadenopathy occurs commonly in viral conjunctivitis but is rare in bacterial conjunctivitis. Gonococcal and chlamydial infections are exceptions that may present with tender lymphadenopathy.

## Membranes

Copious discharge and membrane formation on the inner aspect of the eyelids occur in severe adenoviral and gonococcal infections. In conjunctivitis due to *Streptococcus pyogenes* and diphtheria, two other causes of membranous conjunctivitis, attempts at membrane removal may result in bleeding.

## Diagnostic tests

Routine investigations are not indicated in conjunctivitis unless there is severe inflammation, presence of membranes or follicles or chronicity. Neonatal conjunctivitis is a notifiable disease which needs investigation.

The following are some useful investigations.

### 1. Direct smear

Conjunctival scrapings for Gram stain are indicated in severe infections with copious discharge and in neonatal conjunctivitis. Intracellular Gram-negative diplococci are seen in gonococcal infections. In chlamydial conjunctivitis, Giemsa stain of conjunctival scrapings show basophilic intra-cytoplasmic inclusion bodies in epithelial cells and polymorphonuclear leucocytes.

### 2. Conjunctival swab for culture and antibiotic sensitivity test (ABST)

ABST is useful in identifying the causative organism in suspected bacterial infection and in selection of antibiotics.

### 3. Immunofluorescence test or enzyme immuno-sorbent assay

This test is useful to confirm the diagnosis of chlamydial infection.

### 4. Polymerase chain reaction

Used in the detection of adenovirus, *Herpes simplex* and *Chlamydia* infection.

## Treatment of conjunctivitis

### Viral conjunctivitis

Treatment is mostly symptomatic with artificial tears and cool compresses several times a day. Oral vasoconstrictors or antihistamine drugs are indicated for severe itching. Patient needs reassurance and advice on prevention of further spread.

## Bacterial conjunctivitis

### Gonococcal conjunctivitis

Ceftriaxone 1 gram (im.), or in penicillin allergy oral ciprofloxacin 500 mg in a single dose should be given. Topical antibiotics include fusidic acid, gentamicin and tobramycin.

Eye irrigation with physiological saline to eliminate the discharge is helpful. Entire cornea should be examined for ulcers, which are known to perforate rapidly. If an ulcer is present the patient should be promptly referred to an ophthalmologist.

Possible co-infection with *Chlamydia* should be treated with oral azithromycin 1g single dose or doxycycline 100 mg bid for 7 days (1). Sexual partners also need screening and treatment.

### Non-gonococcal bacterial conjunctivitis

Most cases of acute bacterial conjunctivitis resolve spontaneously. So treatment of bacterial conjunctivitis with topical antibiotics is controversial. According to a Cochrane systematic review and meta-analysis update on acute bacterial conjunctivitis, topical antibiotics are associated with significantly improved rates of early (days 2-5) clinical remission (3). However, this benefit is marginal for later remissions (days 6-10).

Topical antibiotic therapy with a broad spectrum antibiotic drop during the day and an ointment at night can be used. Before instilling the topical medications it is important to clean all traces of discharge from the eye. Options in topical antibiotics include fusidic acid, chloramphenicol, ciprofloxacin and tobramycin.

Fusidic acid, a viscous suspension, is active against Gram-positive organisms (*Staphylococcus*, *Streptococcus*) but not against Gram-negatives. Chloramphenicol has a broad spectrum of activity.

Fluoroquinolones have a wide range of bactericidal activity against most Gram-negative and Gram-positive organisms, by interfering with bacterial DNA synthesis but anaerobes and some strains of *Pseudomonas* are resistant. During pregnancy and lactation topical antibiotic treatment should be used with caution.

Tobramycin is an aminoglycoside with a good coverage over Gram-negative organisms. Although the systemic side-effects are rarely seen in topical antibiotic therapy, allergy could be a problem.

### **Chlamydial conjunctivitis**

Adult chlamydial conjunctivitis, a sexually transmitted disease caused by *Chlamydia trachomatis* serotypes D to K, presents with a subacute unilateral or bilateral mucopurulent discharge. If untreated symptoms may persist for 3-12 months.

Treatment with topical tetracycline ointment q.i.d. for 6 weeks and systemic therapy with azithromycin 1 gram as a single dose or doxycycline 100 mg b.i.d. for 1-2 weeks is recommended. Erythromycin 500 mg q.i.d. for 1 week can be an alternative if tetracycline is inappropriate (4).

### **Allergic conjunctivitis**

Allergic rhinoconjunctivitis and vernal keratoconjunctivitis are the two common forms.

Treatment of allergic conjunctivitis includes conservative measures such as allergen avoidance, cold compressions as well as pharmacotherapy (5).

Topical treatment with mast-cell stabilisers (sodium cromoglicate, lodoxamide), antihistamine drops (levocabastine) and nonsteroidal anti-inflammatory agents (diclofenac sodium, ketorolac tromethamine) are recommended.

Treatment with vasoconstrictors and oral antihistamines can be supplementary. In addition, use of tear supplements will aid in lubrication as well as washout of the allergen.

Topical steroids are indicated in vernal keratoconjunctivitis mainly in the presence of keratopathy. In severe

cases a short course of topical corticosteroids is often required. However, due to side-effects such as ocular hypertension and immune-suppression, corticosteroid therapy should only be administered under the supervision of an ophthalmologist.

**When conjunctival inflammation is associated with severe pain, photophobia, corneal haze or opacity, or diminished vision, urgent referral to an ophthalmologist for further evaluation is mandatory.**

### **Further reading**

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# New guidelines for the management of patients with malaria in Sri Lanka

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## Introduction

The reported number of malaria cases in Sri Lanka has reached an all-time low since 1963. During the year 2007, 196 cases of malaria were reported in the country, of which 189 were vivax and 7 were falciparum infections. The reduction reported in 2007 was the result of a gradual reduction in malaria cases over the last 7 years.

Two parasite species continue to be reported from the country *ie.* *Plasmodium vivax* and *Plasmodium falciparum*. In 2007, 96.5% of the infections reported were *Plasmodium vivax* infections and 3.5% were *Plasmodium falciparum* infections. Over 50% of the falciparum infections reported in 2007 were acquired outside Sri Lanka.

In view of the high proportion of imported falciparum malaria reported now in Sri Lanka, the Ministry of Healthcare and Nutrition has decided to change the guidelines for treatment of malaria infections. This change is also in keeping with recommended WHO guidelines for the management of falciparum infections. Importantly, the National Malaria Control Programme is currently planning to launch a malaria elimination programme with the objective of eliminating indigenous transmission of malaria by the year 2015.

## Diagnosis of malaria infections

The low number of malaria cases reported during the past several years has resulted in clinicians and laboratory services not being adequately careful in suspecting and detecting malaria infections. Sri Lanka is a tropical country where environmental conditions are suitable for the breeding of malaria vectors, and it is important to suspect malaria infections in febrile patients who have been to malarious areas or are engaged in occupations that could expose them to malaria. This is particularly so with regard to all security forces personnel and also residents and visitors to the northern districts of Sri Lanka. All febrile patients who are security forces personnel or residents or visitors from the Northern Province should be investigated for malaria infection by examination of peripheral blood smears or by testing for malaria antigens using rapid diagnostic tests. Treatment of malaria infections without laboratory confirmation should be avoided as far as possible, and every effort should be taken to confirm diagnosis through laboratory investigations.

If a trial of treatment with antimalarials is being undertaken on clinical grounds after repeated investigations have been negative for malaria infection, it is recommended that blood smears of such patients are obtained and preserved for cross-checking by the Anti-Malaria Campaign Central Parasitology Laboratory. It is also recommended that only chloroquine be used in such situations. However, intravenous quinine may be used in critically ill patients as a life-saving measure.

## Management and treatment of vivax infection

The management of *Plasmodium vivax* infections remains unchanged.

The objective of treating vivax infections is to ensure early radical cure and prevention of relapses. Early treatment will prevent secondary cases. Following laboratory confirmation of *Plasmodium vivax* infection, all patients should be given a course of chloroquine (base) at a dose of 25 mg/kg over three days. This dose should be divided as 10 mg/kg as a single dose on the first and second days followed by a dose of 5 mg/kg on the third day. Unless primaquine is contraindicated, all vivax infected patients should be given a course of primaquine (base) at a dose of 0.25 mg/kg daily over a period of 14 days.

Primaquine is not recommended during pregnancy, to infants under one year of age, and to patients with G6PD deficiency.

## Management and treatment of uncomplicated falciparum infection

All patients with a laboratory confirmed diagnosis of uncomplicated falciparum malaria infections should be treated with artemisinin based combination therapy (ACT) and primaquine. They **should be admitted to a hospital** where ACT is available. The ACT treatment selected for use in Sri Lanka is a tablet containing artemether 20 mg and lumefantrine 120 mg having the trade name Coartem<sup>®</sup>. In this article where the term ACT is used it means Coartem<sup>®</sup>. ACT is not recommended for children whose body weight is less than 5 kg.

Ready to use colour coded blister packs of Coartem<sup>®</sup> are available to cover 4 weight ranges. All the tablets

contained in the weight appropriate pack should be given to the falciparum infected patient under supervision over three days. The yellow coded blister pack contains 6 tablets and is for administration to children with a body mass of 5-15 kg. The blue coded blister pack contains 12 tablets and is to be given to children weighing 15-25 kg. The orange coded blister pack containing 18 tablets is for patients weighing 25-35 kg and the green coded blister pack containing 24 tablets is for patients weighing > 35 kg. These tablets should be given as shown in the table.

A weight appropriate single dose of primaquine (0.75 mg/kg) should be given after completion of the ACT regime before discharge from hospital to destroy gametocytes.

In children weighing less than 5 kg, it is recommended that parenteral quinine dihydrochloride be given at a dose of 10 mg/kg body weight in the form of a slow infusion over a period of 4 to 6 hours diluted in 5% dextrose to be repeated at 8 hourly intervals. Quinine therapy should be continued for at least 7 days.

Uncomplicated falciparum infections during pregnancy should be treated with ACT during the second and third trimesters. Pregnant women with uncomplicated falciparum malaria in the first trimester of pregnancy should be treated with oral quinine sulphate 10 mg/kg body weight at 8-hourly intervals for 7 days. Primaquine is not recommended during pregnancy.

ACT should not be given to lactating mothers who are breast feeding children less than 5 kg in weight. Such

mothers with falciparum infections should also be treated with oral quinine sulphate in the dosage indicated above.

**Antimalarials for patients with uncomplicated mixed infections caused by *Plasmodium vivax* and *Plasmodium falciparum***

These patients should be treated with the weight appropriate dose of ACT followed by the usual dose of primaquine for the radical treatment of *Plasmodium vivax* infection over 14 days. They should also be treated in hospital for a minimum of 3 days.

**Antimalarials for patients with severe and complicated *Plasmodium falciparum* infections**

Most patients diagnosed as having severe and complicated falciparum malaria require immediate parenteral administration of effective antimalarial agents. The immediate issue at hand would be saving the patient's life with rapid clearance of parasitaemia, and this can be accomplished only through intravenous administration of fast acting antimalarials. The treatment of choice should be parenteral administration of quinine dihydrochloride 10 mg/kg by slow intravenous infusion in 5% dextrose solution over 4 to 6 hours, repeated every 8 hours until the patient is able to take oral medication. After the condition of the patient has improved and the patient is capable of taking oral medication, all patients, excluding children weighing less than 5 kg, should be given the weight appropriate full course of treatment with ACT followed by a single dose of primaquine.

**Table. Dosage schedule of ACT tablets for different weight ranges**

| <i>Time<br/>(Hours)</i> | <i>Number of ACT tablets to be administered</i> |  |  |   |
|-------------------------|---|--|--|---|
|                         | <i>Children<br/>5-15 kg<br/>(Yellow pack)</i>   | <i>Children<br/>15-25 kg<br/>(Blue pack)</i> | <i>Adults<br/>25-35 kg<br/>(Orange pack)</i> | <i>Adults<br/>over 35 kg<br/>(Green pack)</i> |
| 00                      | 1   | 2  | 3  | 4   |
| 08                      | 1   | 2  | 3  | 4   |
| 24                      | 1   | 2  | 3  | 4   |
| 36                      | 1   | 2  | 3  | 4   |
| 48                      | 1   | 2  | 3  | 4   |
| 60                      | 1   | 2  | 3  | 4   |
| Total                   | 6   | 12   | 18   | 24  |

ACT= Coartem®

Patients having early signs of severe and complicated falciparum malaria but capable of taking oral medications should be treated with the weight appropriate dose of ACT followed by a single dose of primaquine. They should be treated in hospital for a minimum of 3 days.

Severe and complicated falciparum malaria infections in the second and third trimester of pregnancy should be treated with parenteral quinine as above, and after clinical improvement, with the weight appropriate dose of ACT. Severe and complicated falciparum malaria in the first trimester of pregnancy should be treated with parenteral quinine until clinical improvement, followed by oral quinine for a total of 7 days in the appropriate doses.

All malaria patients should be detected early and treated appropriately. This is critically important today as immunity levels in the population have decreased owing to low transmission rates during the last several years, and also to facilitate a successful elimination programme. Clinicians must notify the Anti-Malaria Campaign or the respective regional officers of the campaign regarding all malaria cases detected. The Anti-Malaria Campaign has provided adequate stocks of ACT to all medical institutions with laboratory facilities.

The Anti-Malaria Campaign Directorate may be contacted on telephones (011) 2581918/2588408/2368173/2368174 or Fax (011) 2368885 for further details.

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## Runny nose: allergic rhinitis

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The nose is lined by mucosa which produces mucus as a protective mechanism of the upper airway. If the tissue is irritated it becomes inflamed and swollen, causing blockage and secretion of a lot of mucus leading to running nose.

Short term runny nose with fever is commonly caused by viral infections (common cold or coryza). A runny nose continuing more than a week is considered chronic, and needs proper diagnosis and management. Over 90% are due to allergic rhinitis and the rest includes vasomotor rhinitis and rare conditions.

Runny nose is accompanied by several other symptoms such as chronic cough from postnasal drip, and headache resulting from sinusitis.

### **Allergic rhinitis**

Allergic rhinitis occurs when inhaled allergens interact with IgE antibodies on cells in the airway. It is a common disorder, affecting up to 40% of people in Australia and New Zealand. Its prevalence has doubled over the past

25 years. Estimates of the prevalence of allergic rhinitis in the United States range from 8.8% to 16%. A survey of six thousand patients attending the OPD at the Teaching Hospital, Ragama revealed allergic manifestations in 8.8% patients, and 22% of them had rhinitis.

### **Seasonal allergic rhinitis**

Seasonal (or intermittent) allergic rhinitis (often referred to as hay fever) is triggered by wind borne pollen most commonly from grasses, weeds and sometimes trees. This is seen during spring and summer in countries with seasonal changes.

### **Perennial allergic rhinitis**

Perennial (or persistent) allergic rhinitis occurs throughout the year and is commonly triggered by exposure to house dust mites. Symptoms are usually worse early morning or at night. Animal dander (especially cat) and mould spores may trigger similar symptoms. We have found that house dust mites and cockroaches are the two most important allergens involved with wheezing in Sri Lanka.

## Symptoms of allergic rhinitis

Most cases of allergic rhinitis begin in the teens or early adult life and improve by the fourth or fifth decade of life. Symptoms include sneezing, itching and copious, thin, watery discharge from the nose. Nasal obstruction is also common, particularly in perennial rhinitis. Symptoms are less common in infants and young children. When they do occur, nasal obstruction may interfere with feeding and contribute to irritability.

Far from being a trivial illness, untreated or inappropriately treated allergic rhinitis has a significant effect on quality of life eg. poor quality sleep, fatigue, daytime sleepiness, mood changes, and poor work performance, and can last for several years. Severe allergic rhinitis can also:

- make asthma more difficult to control
- make people more prone to sinus infections
- impair learning and behaviour in children
- result in bad breath, a husky voice and sore throats
- worsen snoring and the tendency to have sleep apnoea in adults
- result in eye infections because people rub itchy eyes, and
- cause abnormal development of the mouth and teeth from chronic mouth breathing.

## Evaluation

### History and physical examination

The history helps to establish the seasonality, year-to-year persistence, potential inciting factors, and complicating conditions such as sinusitis, nasal polyps, and asthma. These conditions occur more frequently in patients with allergic rhinitis than in control populations; in one study, 19 to 38% of patients with allergic rhinitis were found to have coexisting asthma. The diagnosis can generally be made on the basis of the history and physical examination. The examination should note signs of rhinitis and conjunctivitis, and may reveal wheezing suggestive of associated asthma. Spirometry is useful in detecting subclinical asthma and computerised tomography most reliably reveals sinusitis in patients with symptoms of refractory rhinitis. Additional testing will be helpful if the diagnosis is uncertain or if the response to therapy is suboptimal. For example, blood or nasal eosinophilia suggests an allergic cause, whereas neutrophilia points to an infectious cause.

## Taking the history is important

Important information includes:

- the type and duration of symptoms
- whether they are perennial or seasonal
- whether there is any seasonal exacerbation
- aggravating and relieving factors
- use and compliance with medication
- other intercurrent allergic disease eg. asthma, atopic dermatitis
- family history
- occupation and hobbies
- home and work environments and
- the presence or absence of systemic symptoms.

## Differential diagnosis

A common problem in patients is the distinction between allergic rhinitis and infections such as common cold or sinusitis. In allergic rhinitis, watery rhinorrhoea tends to persist and itching of the nose, eyes, palate and ears are more prominent.

Infections due to rhinovirus may result in thickened or discoloured secretion, but symptoms rarely persist beyond a week.

Sinusitis should be suspected with prolonged symptoms such as discoloured nasal discharge or postnasal drip, particularly when associated with bad taste or bad breath, impaired sense of smell, facial pain, cervical lymphadenopathy or recurrent sore throat.

## Allergic rhinitis should be considered in patients with:

- continuous or recurrent upper respiratory infections
- frequent sore throats
- mouth breathing and snoring
- heaviness over the sinuses
- recurrent infective sinusitis
- headaches, and
- recurrent upper respiratory tract or middle ear infections, particularly in children.

## Other causes of rhinitis

### Common

- Non-allergic (vasomotor) rhinitis
- Sinusitis
- Recurrent upper respiratory tract infection (particularly in young children)

### Less common

- Anatomical abnormalities eg. nasal septal deviation
- Nasal polyps
- Foreign bodies (particularly in young children)
- Pregnancy
- Hypothyroidism
- Medication eg. antihypertensive agents, oral contraceptive pill
- Rhinitis medicamentosa (due to abuse of topical decongestant sprays)
- Occupational rhinitis (eg. animal exposure, wood dusts, industrial enzymes, food processing, latex)

### Rare

- Malignancy
- Vasculitis (eg. Wegeners granulomatosis)
- Sarcoidosis
- Atrophic rhinitis
- Cocaine abuse

## Allergy testing

Allergy testing is performed to confirm which allergens are relevant to the symptoms and which should be included in immunotherapy regimens. Culpable allergens can be identified by skin or in vitro tests for the presence of allergen-specific IgE antibodies. A patient with an annual recurrence of symptoms is likely to be reacting to seasonal pollen or other environmental triggers. Allergens contained in dust mite excreta, in the epidermis and saliva of furred pets, in cockroach bodies, and in fungal spores are present throughout the year.

## Management of allergic rhinitis

Treatment strategies depend on modulation of the immune response by interfering with the function of IgE antibodies, interruption of the release of antigen-induced autacoids (histamine and eicosanoids) from IgE-sensitised cells, inhibition of the autacoid effect at

receptor sites, and the resolution of allergic inflammation. Although there are no cures for allergic rhinitis, symptoms can be effectively prevented or suppressed. Options include:

- avoidance of allergic triggers
- medication (topical and oral)
- non-medicated treatment
- immunotherapy

## Avoidance of allergic triggers

The first step in the management of allergic rhinitis is to identify the cause(s) of the problem, and then to remove or avoid the cause(s) where possible. Neither medications nor immunotherapy are substitutes for reducing exposure to allergic triggers.

In some cases a cause may be obvious (eg. pet allergies). In others it may be necessary to perform allergen testing (skin prick testing or serum specific IgE panel) to find the offending allergen.

## Medication

### Topical medication

*Corticosteroid nasal sprays* (beclomethasone) are effective in the management of allergic rhinitis, particularly in people with severe and prolonged symptoms and when congestion is an important symptom. They relieve nasal blockage, discharge, sneezing, nasal itch, post-nasal drip and eye symptoms. Corticosteroid nasal sprays act as prophylactic agents and are not intended to relieve acute symptoms, hence they need to be used on a regular basis. Once control of symptoms has been achieved the dose should be reduced to the minimum required to control symptoms. Daily use is required in most patients.

Nasal corticosteroids have relatively few adverse effects. The most common one is epistaxis, which occurs in 10% of cases and rarely requires discontinuation of the drug. Uncommon effects include delay in the attainment of normal height in children using intranasal beclomethasone and increased intraocular pressure and posterior subcapsular cataracts in adults.

*Antihistamine nasal sprays and eye drops* act rapidly (within minutes) to relieve sneezing or itching and are generally well tolerated. In general, they are less effective in relieving severe nasal congestion.

*Decongestant nasal sprays or drops* (oxymetazoline) provide quick relief, but should only be used in short term (up to a maximum of 5 days) to clear excessive

nasal blockage. In patients with severe nasal obstruction, they may be used for a few days to open the air passages to allow access to the nasal mucosa by corticosteroid nasal sprays. Repeated or long term use of nasal decongestant sprays can lead to rebound swelling of nasal mucosa with the need to use ever increasing amounts of medication. This condition is known as rhinitis medicamentosa and it can eventually lead to atrophic rhinitis.

**Anticholinergic sprays** (ipratropium bromide) are very effective in reducing watery rhinorrhoea.

**Mast cell stabilising nasal sprays or eye drops** (sodium cromoglicate) reduce inflammation with regular use.

### Oral medication

**Antihistamines** were introduced more than 50 years ago for the treatment of allergic rhinitis. However, although these first-generation antihistamines are clinically effective, their use is limited by their anticholinergic and sedative effects, such as impaired performance of tasks. More recently, second-generation antihistamines lacking substantial sedative properties have largely supplanted the earlier drugs. Antihistamines substantially reduce symptoms of nasal itching and watery eyes and have moderate but clinically and statistically significant effects in reducing rhinorrhoea and sneezing. However, these agents have minimal effects on the symptom of nasal congestion.

**Decongestant (pseudoephedrine or phenylephrine) tablets** will unblock and dry the nose. They should be used with caution in patients with hypertension, angina, prostatism and thyrotoxicosis. They are contra-indicated in patients taking monoamine oxidase inhibitor antidepressants. Side-effects include restlessness, insomnia, and tachyarrhythmias.

**Combination drugs containing antihistamines and decongestants** provide greater symptomatic relief than antihistamines alone, particularly when nasal congestion is a prominent symptom. However, as they contain decongestants, the same cautions, contra-indications and side-effects apply to them.

**Systemic corticosteroids** are indicated for allergic rhinitis only in exceptional circumstances, where there is intense irritability or severe obstruction of the nose. They should only be used short term under medical supervision.

**Leucotriene-receptor antagonists** (montelukast) have been used in some studies with limited success, either alone or in combination with antihistamines. Although topical nasal steroids appear to provide superior

symptoms control, these drugs may provide additional relief in selected patients.

**Mast cell stabilisers** have proved to be significantly better than placebo at reducing nasal symptoms in some trials, but data are inconsistent, and its effects are modest.

### Ophthalmic preparations

The mast-cell stabilisers, ocular antihistamines, and the nonsteroidal antiinflammatory drug ketorolac are all used topically in ophthalmic preparations for allergic conjunctivitis. Randomised, controlled trials have demonstrated that these agents significantly reduce ocular symptoms, including itching, and improve sleep. For predominantly ocular symptoms, one of these preparations alone may suffice.

### Non-medicated treatment

**Steam and salt water (saline) sprays** used on a regular basis can help to relieve nasal blockage and thick secretions. Nasal irrigation with saline is an adjuvant therapy in view of reducing side-effects, such as drowsiness and dry mouth.

### Diet and rhinitis

Diet has only a minor influence on symptoms in most people. The results from strict "elimination diets" are usually disappointing and may affect nutrition. Despite common mythology, there is no good evidence that "milk makes mucus", or that milk worsens either hay fever or asthma. Nasal symptoms may sometimes occur after hot or spicy food or alcohol. This is called "gustatory rhinitis". It appears to be a reflex phenomenon, resulting from stimulation of nerve endings that trigger glands to secrete more mucus. Anticholinergic nasal spray is often effective, particularly if used before eating.

### Immunotherapy

Immunotherapy (desensitisation) is the closest thing to a cure for allergic rhinitis and an effective adjunct to drug therapy in selected patients. It should be prescribed only by allergy specialists and only after allergen avoidance and drug treatment have been instituted. Immunotherapy involves the administration of gradually increasing amounts of allergic material, usually given to patients by injection over a period of years. These allergen injections alter the way in which the immune system reacts to allergens, by "switching off" allergy. The end result is that patients become "immune" to the allergens, so that they can tolerate them with fewer or no

symptoms. Immunotherapy is often recommended for treatment of allergic rhinitis (and sometimes asthma) when;

- symptoms are severe
- the cause is difficult to avoid (eg. grass pollen)
- medications are unhelpful or cause adverse side-effects and patients need medication most days.

### Summary

Mild symptoms of allergic rhinitis are easily relieved with an oral antihistamine or a nasal corticosteroid alone. For patients with moderate-to-severe symptoms of allergic rhinitis with nasal congestion as a predominant finding, therapy should generally be started with the daily use of a nasal corticosteroid, which could be combined with a second-generation oral antihistamine. Therapy should be started before the anticipated appearance of allergens and continue during the time of likely exposure. If eye symptoms persist, an ocular antihistamine could be added.

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## Antiepileptic drugs in pregnancy and lactation

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### Summary

**No antiepileptic drug is completely safe to use in pregnancy as the risk of fetal abnormality is increased. Valproate should be avoided if possible because of the risk of major malformations. Ideally a plan for managing the woman's epilepsy during pregnancy should be prepared before conception. The occurrence of an unexpected pregnancy should not trigger sudden cessation or alteration of antiepileptic drug treatment without medical advice. The smallest effective dose of a drug with a low risk of teratogenicity should be used. Doses may need adjustment as the pharmacokinetics of some drugs change during pregnancy. Data are limited, but most antiepileptic drugs seem to have little effect on full-term breastfed babies.**

Key words: birth defects, folate, valproate, vitamin K.

(*Aust Prescr* 2008; 31: 70-2)

### Introduction

Uncontrolled epilepsy in a pregnant woman is a serious and potentially life-threatening condition for both mother and child. Most pregnant women with epilepsy will need to take at least one antiepileptic drug. The goal for all concerned is a healthy, seizure-free mother and an undamaged child. The following somewhat contradictory issues need to be considered concurrently.

- The optimum treatment of the mother's epilepsy requires that the most appropriate antiepileptic drug be used in effective doses throughout pregnancy. This requires knowledge of specific epileptic syndromes and also antiepileptic drug pharmacokinetics before, during and after pregnancy.

- Any adverse effect that the antiepileptic drug could have on the developing child needs to be avoided or minimised during pregnancy and lactation.

### **Fetal abnormality**

Women with epilepsy taking antiepileptic drugs have a greater (2-3 times) risk than other women of having a baby with a fetal abnormality. Taking more than one antiepileptic drug carries a higher risk than monotherapy. Major malformations, such as congenital heart disease, neural tube defects, urogenital defects and cleft lips or palates, occur in about 3-7% of women with epilepsy who take antiepileptic drugs, although a substantially higher risk is attributed to high doses of valproate (greater than 1400 mg/day).

For more than 30 years, a gradually increasing body of literature has attributed a 'fetal anticonvulsant syndrome' and increased malformation rate to all the 'old' antiepileptic drugs – barbiturates, phenytoin, carbamazepine and valproate. Some data are now available for lamotrigine, but very little is known of the risk of the 'new' antiepileptic drugs such as levetiracetam, topiramate, oxcarbazepine, gabapentin, pregabalin, tiagabine and zonisamide.

Problems may emerge in childhood. Numerous small studies have suggested cognitive and language impairment and an increase in autistic spectrum disorder in children who have been exposed to antiepileptic drugs *in utero*<sup>1</sup>. Recent reports suggest that these problems may be highest in children who have been exposed to valproate.

In order to better understand the extent of the teratogenic risks of all antiepileptic drugs, observational pregnancy registers have been established around the world including Australia.\* These registers contain useful information about the most commonly used antiepileptic drugs. From these registers, consistent warnings about the increased risk of structural birth defects have been issued for valproate. The North American Pregnancy Register has published specific concerns with respect to phenobarbitone and lamotrigine.

### **Management of women with epilepsy**

Before conception, a comprehensive management plan is desirable. The diagnosis of epilepsy needs to be validated, the epilepsy syndrome elucidated, 'optimal' antiepileptic drug treatment established and folate supplements given.

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\* Australian Pregnancy Register for women on antiepileptic medication. Phone 1800 069 722.

Potential parents should understand that there are no 'safe' antiepileptic drugs in pregnancy. The balance of risks, as presently known, should be explained to them. All risk of harm cannot be eliminated.

Women with epilepsy who are considering pregnancy should be treated with the least teratogenic but most efficacious antiepileptic drug for their particular type of epilepsy at the lowest effective dose. Pregnancy counselling and planning are strongly advised. When an unexpected pregnancy happens and embryogenesis has already occurred, there is usually little to gain and there may be substantial risk in stopping or changing antiepileptic drugs. Early monitoring for an adverse fetal outcome and appropriate counselling are advisable.

### **Folate and vitamin K<sub>1</sub>**

All women are recommended to take folate supplements before pregnancy. It is reasonable practice to recommend routine folate supplementation, 0.5-1.0 mg/day, to all potentially reproductive women with epilepsy taking antiepileptic drugs even if they are not contemplating pregnancy. It is currently recommended that a woman with epilepsy takes folate 5 mg/day for three months before conception and for at least the duration of the first trimester. There is good evidence that folate supplementation reduces the risks of spina bifida and other malformations in large population studies, but there is no documented evidence that it further reduces teratogenic risk in women taking antiepileptic drugs.

National Health and Medical Research Council Guidelines (2000) recommend that all babies at birth are given 1 mg intramuscular vitamin K<sub>1</sub> or a course of oral vitamin K<sub>1</sub>. Maternal oral vitamin K<sub>1</sub>, for example 10 mg/day for one month prepartum, has been recommended when enzyme-inducing antiepileptic drugs are prescribed because the drugs may potentially predispose the baby to haemorrhagic disease of the newborn. However, reports suggest that this risk is practically negligible<sup>2</sup>.

### **Specific epilepsy syndromes**

Two major groups of epilepsies need to be distinguished because they typically respond differently to different drugs. Localisation-related or partial epilepsies respond to most antiepileptic drugs. For idiopathic generalised epilepsy valproate is usually the most effective drug. Often, especially in juvenile myoclonic epilepsy, seizures can be controlled with a reasonably low valproate dose, for example 800 mg/day or less. Lamotrigine may be helpful but often is not as effective as valproate and

sometimes worsens the myoclonic seizures of juvenile myoclonic epilepsy. Topiramate and levetiracetam may be effective in idiopathic generalised epilepsy while carbamazepine, tiagabine, oxcarbazepine, phenytoin and gabapentin may worsen some seizure types, especially myoclonic and absence seizures. For some women with idiopathic generalised epilepsy syndromes, there may be no effective alternative to valproate.

### **Drug exposure and effects**

The pharmacokinetics of antiepileptic drugs may change in pregnancy. Doses have to balance the risk of seizures with minimising the risk of harming the fetus.

#### ***Valproate***

Four pregnancy registers and numerous smaller studies have warned that there is a substantial risk of major malformations including spina bifida when valproate is used as monotherapy or with other drugs. The Australian Pregnancy Register<sup>3</sup> has reported the risk to be as high as 16% for first trimester fetal exposure to valproate at doses above 1400 mg/day, compared with 6% at doses below 1400 mg/day. Others have reported higher risk when plasma valproate concentrations are consistently high (more than 70 mg/L). Valproate should therefore be avoided in reproductive women wherever possible. When it is unavoidable, the lowest effective dose should be used. It should not exceed 1000 mg/day in divided doses. The woman needs to be warned of the risk of seizures and she should avoid seizure triggers such as sleep deprivation. While she is taking a reduced dose she may have to restrict her driving.

If the valproate dose has been reduced to a minimum during pregnancy in order to reduce teratogenesis, the postpartum effective dose may need to be re-established before the onset of labour. This is a time of increased seizure risk especially in patients with idiopathic generalised epilepsy who are very sensitive to sleep deprivation.

Breastfeeding is considered compatible with valproate therapy. Valproate concentrations in breastfed babies are low.

#### ***Lamotrigine***

The North American Pregnancy Register has reported that exposure to lamotrigine in the first trimester may cause an increased risk of oral clefts (a rate of 8.9 per 1000, as compared to 0.37 per 1000 in the reference

population)<sup>4</sup>. Significant close related teratogenesis with lamotrigine exceeding 200 mg/day has been reported<sup>5</sup>. Lamotrigine clearance increases steadily through to 32 weeks of pregnancy. Plasma concentrations of lamotrigine fall early in pregnancy so dose increases may be necessary to control seizures. A trough plasma lamotrigine concentration before pregnancy, at the onset of the second trimester of pregnancy and every two months during pregnancy may help to guide any necessary increase in lamotrigine dose. Postpartum, the lamotrigine concentration rises within a few days and prompt dose reduction may be required to prevent toxicity<sup>6</sup>.

Lamotrigine is excreted in considerable amounts into breast milk. Early reports show that most full-term babies seem to have little problem with breastfeeding, but close monitoring for toxicity, especially in small or preterm babies, is advised.

#### ***Carbamazepine***

For almost 20 years reports have associated carbamazepine with an increased risk of structural birth defects including spina bifida. However, no pregnancy register has yet shown any statistically significant increase in risk relative to the total population. In the Australian Pregnancy Register, the malformation rate with carbamazepine cannot be distinguished from that of women with epilepsy who are not taking antiepileptic drugs. Modest pharmacokinetic changes occur during late pregnancy, but dose changes are not usually required. Carbamazepine is compatible with breastfeeding in the full-term infant.

#### ***Phenytoin***

Phenytoin is now used less frequently in women with epilepsy. It has been reported to produce an increase in major malformations.

A marked increase in the clearance of phenytoin in pregnancy is associated with a fall in plasma concentrations and possible loss of seizure control. Regular monitoring of plasma concentrations throughout pregnancy helps to determine when a higher dose is required. Postpartum monitoring helps prevent phenytoin toxicity. The pharmacokinetic changes of early pregnancy and postpartum occur more slowly with phenytoin than with lamotrigine. Breastfeeding is acceptable with phenytoin.

### **Levetiracetam**

Levetiracetam has been used in few pregnancies. Its teratogenic risk is unknown.

There appears to be a substantial increase in clearance during pregnancy and an associated fall of blood concentrations<sup>7</sup>. It is not yet known if this is associated with a loss of epilepsy control. Serum monitoring is not currently available, but may prove helpful in clinical practice.

Although levetiracetam is secreted into breast milk, recent data suggest that the neonatal concentrations are low. Breastfeeding is probably acceptable in full-term neonates, but close clinical monitoring is advisable.

### **Clonazepam**

Clonazepam is used as an adjunctive antiepileptic drug. No particular pregnancy risks have been associated with it, but it may cause drowsiness in the breastfed neonate. Withdrawal effects can occur if breastfeeding ceases suddenly.

### **Oxcarbazepine, topiramate, ethosuximide**

Only a few pregnancies have been documented, so the teratogenic risks of these drugs are unknown. Oxcarbazepine clearance seems to increase significantly in pregnancy, but the clinical importance of this is uncertain.

These drugs are excreted in breast milk, but the very limited data available suggest that neonatal drug concentrations are usually low. Breastfeeding is probably acceptable with clinical monitoring.

### **Phenobarbitone**

Phenobarbitone is rarely used now in Australia in reproductive women with epilepsy. The North American Pregnancy Register suggests that it may carry a significant teratogenic risk. A marked increase in plasma clearance occurs in pregnancy. Phenobarbitone in breast milk may cause neonatal drowsiness and apathy.

### **Conclusion**

In women with epilepsy treated with antiepileptic drugs, there is a better than 90% chance that the child will be normal. The most specific therapeutic dilemma and the highest risk is in women who need to take valproate to control their epilepsy. Most infants whose mothers are taking antiepileptic drugs can be successfully breastfed without complications.

*Editorial note:* Some antiepileptic drugs are used in the management of bipolar disorders. See: Sved Williams A. Antidepressants in pregnancy and breastfeeding. *Aust Prescr* 2007; **30**: 125-7.

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***Current information about drug registration***

New chemical entities registered

| <b>Generic name</b> | <b>Brand name</b> | <b>Dosage form</b>                | <b>Manufacturer</b>   | <b>Importer</b>     | <b>Therapeutic class / use(s)</b>               |
|---------------------|-------------------|-----------------------------------|-----------------------|---------------------|---|
| Nimotuzumab         | BIOMab EGFR       | Injection, 50 mg /10 ml           | Biocon, India         | ABC Pharma Services | Anticancer                                      |
| PAdefovir           | Adesera           | Tablet, 10 mg                     | Cipla, India          | Citihealth Imports  | Chronic hepatitis B                             |
| Ranibizumab         | Lucentis          | Intravitreal injection<br>10mg/ml | Novartis, Switzerland | Baurs               | Neovascular age-related<br>macular degeneration |

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