

## Prophylaxis of conjunctival infections in newborn infants

**UPDATE**

## Introduction

This update concerning the prophylaxis of conjunctival infections in newborn infants was drawn up due to the withdrawal from market, for industrial reasons in December 2008, of the FAURE proprietary pharmaceutical 1% "SILVER NITRATE" Eye Drops solution, single-dose container..

This product granted a Marketing Authorisation (MA) for France in 1981 for the indication: "preventive treatment of conjunctival infection in newborn infants, as a single administration to each eye immediately after birth." These were the only eye drops in France presenting a specific indication for this neonatal prophylaxis, focused on the prevention of gonococcal infection. It should be noted that the instillation of silver nitrate-based eye drops caused chemical conjunctivitis in between 50 and 90% of cases.

In the 19th century, neonatal gonococcal infections were very widespread (approximately 10% of newborn infants in Europe) and the sequelae were dreadful (corneal impairment and blindness in 20% and 3% of cases respectively). The systematic use of silver nitrate-based eye drops, one drop in each eye of newborn infants, recommended by Cr  d   in 1880, led to a significant reduction in the number of gonococcal ophtalmia neonatorum (from 10 to 0.3%). This practice has continued until the present day.

It is now necessary to determine whether the systematic prophylaxis of neonatal conjunctivitis is still justified and what are the causative pathogens.

## Clinical data

Pregnant women with a sexually transmitted infection (STI) may potentially contaminate their children during vaginal labour or, by Caesarean, in case of premature rupture of the amniotic sac prior to surgery.

Currently, *Neisseria gonorrhoeae* and *Chlamydia trachomatis* (more frequent, but less pathogenic) are the two bacteria to take into consideration in the prevention of conjunctival infections in newborn infants as they can potentially lead to severe ocular complications in newborn infants.

Gonococcal contamination can lead in newborn infants to generalized infection, though the most common manifestation is bilateral purulent conjunctivitis. It most frequently appears during the first 2 to 5 days of life. The eyes are severely affected, frequently associated with corneal impairment, with ulceration or opacification. The infection's rapid progression may lead to blindness.

*Chlamydia trachomatis* infection in newborn infants can cause uni- or bilateral conjunctivitis, appearing most frequently between 5 and 14 days after birth. Mucopurulent secretions are of variable severity and the cornea is not generally affected. Progression may be unfavourable, with appearance of keratitis or conjunctival scarring. Severity is frequently lower than that observed with gonococcal infections. If the diagnosis is uncertain, it is recommended to search for *Chlamydia trachomatis* by PCR on initial urine, as serological tests are of little diagnostic value.

## Epidemiological data

An increase in STIs and particularly in gonococcal infections, has been observed in industrialized countries, including France. There are, however, no specific epidemiological data for *Neisseria gonorrhoeae* or for *Chlamydia trachomatis* infections in pregnant women, nor concerning the impact of these specific infections on newborn infants.

It is worth reminding that gonococcal infections in women are most frequently asymptomatic, thus potentially leading to an underestimated number of cases.

The literature data assessing the specific use of prophylactic treatment of gonococcal conjunctival infections of newborn infants are small and provide no strong scientific evidence. The data provided for the efficacy of anti-infectious agents used to prevent Chlamydia trachomatis-related ophthalmia neonatorum are contradictory and do not permit to draw any conclusions.

In this context, the Afssaps conducted 2 prescription surveys based on a simple questionnaire sent, on the one hand to French maternity units and, on the other hand, to European health representatives. The data collected, though non-exhaustive, allowed Afssaps to confirm the existence of heterogeneous practices.

In France, the survey conducted by 17 Regional Pharmacovigilance Centres (RPVC)<sup>1</sup> revealed that:

- 1/3 of the 68 maternities questioned did not use systematic antibiotic prophylaxis;
- for the remaining 2/3, when antibiotic prophylaxis is prescribed, rifamycin is the most frequently used agent. The other products mentioned are: ciprofloxacin, gentamicin, picloxydine and tobramycin.

In Europe, the survey conducted in 28 European Community countries<sup>2</sup> revealed that:

- 1/3 of 22 responding countries do not use systematic antibiotic prophylaxis;
- for 4 countries, the antibiotic prophylaxis is implemented in certain maternity units, or if risk factors are present;
- for the other countries, when antibiotic prophylaxis is implemented, silver nitrate is most frequently used. The other mentioned products are: ampicillin, ciprofloxacin, erythromycin, povidone iodine, tetracyclines and tobramycin.

A distinct North/South gradient can be observed, with no antibiotic prophylaxis in Scandinavian countries.

Considering these data and based on expert opinions, the strategy for the prevention of neonatal conjunctival infections leads us to recommend targeted prophylaxis in newborn infants whose parents are at risk from STIs, i.e. with a prior history of STI and/or STI risk factors.

Non-monitored or poorly monitored pregnancies are considered at risk of STI.

Furthermore, as for all newborn infants, including those not in the at-risk population, physicians should remain vigilant concerning the appearance of neonatal conjunctivitis. A microbiological sample should be able by conjunctival scraping to search specifically for Gonococci or Chlamydia trachomatis when faced with conjunctivitis presenting the following signs:

- abundant purulent secretions;
- severe conjunctival hyperaemia<sup>3</sup>;
- appearance during the first week of life;
- absence of lacrimation except for secretions<sup>3</sup>;
- signs of seriousness (keratitis, hypopyon).

## Therapeutic choice

The therapeutic choice takes into consideration the ophthalmic preparations available in France, their pharmaceutical form, joint spectrum of action against *Neisseria gonorrhoeae* and *Chlamydia trachomatis* and the existence of french acquired antibiotic resistance.

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<sup>1</sup> Question submitted to French RPVCs: Is systematic neonatal conjunctival antibiotic prophylaxis recommended in hospital maternity units and larger private regional maternities? If so, what product is used?

<sup>2</sup> Question asked to national representatives of the European Centre for Disease Prevention and Control: Is systematic neonatal conjunctival antibiotic prophylaxis recommended in your country? If so, what product is used?

<sup>3</sup> In case of congenital tear duct obstruction, the conjunctivitis is accompanied by lacrimation persisting after physiological saline wash.

## Galenical data

Compared to eye drops solution, ophthalmic ointments do not diffuse as readily into the tear ducts and are more difficult to apply to newborn infants.

The eye drops solution ensures a high local concentration of the anti-infectious agent. It is well-suited to neonatal use.

The single-dose presentation is preferable to the multi-dose presentation as it avoids any risk of infectious contamination. If a single-dose presentation is not available, a single multi-dose bottle per child should be used.

## Microbiological data - MA-related information

### Aminosides (gentamicin, tobramycin)

- active *in vitro* against *Neisseria gonorrhoeae*, but not against *Chlamydia trachomatis*.

### Ampicillin (beta-lactam antibiotic of the penicillin group)

- active *in vitro* against *Neisseria gonorrhoeae*, but not against *Chlamydia trachomatis* and no ampicillin-based ophthalmic pharmaceutical product is available in France.

### Cyclins

- active *in vitro* against the two target species, **but** plasmid-borne and chromosomal resistance is currently frequent to *Neisseria gonorrhoeae*. Furthermore, the french Marketing Authorisation (MA) for ophthalmic pharmaceutical product is currently limited to children aged 8 years and above (risk of dental dyschromia).

### Ciprofloxacin (fluoroquinolone antibiotic)

- theoretically active *in vitro* against *Neisseria gonorrhoeae*, **though** the percentage of gonococcal strains displaying high-level resistance is of approximately 40% in France.

### Macrolides

- erythromycin: no ophthalmic pharmaceutical product currently available in France.
- azithromycin: active *in vitro* against the 2 target species and adapted single-dose form, **but** the french MA states that this eye drops solution (indicated for the curative treatment of conjunctivitis) is not intended for the prophylaxis of neonatal conjunctivitis. Furthermore, no studies have been published on children under the age of 1 year and the impact of this antibiotic must not be underestimated (frequently used in certain Northern European countries for the general route treatment of gonococcal urethritis accompanied by the emergence of the first cases of high-level acquired resistance).

### Picloxydine (antiseptic)

- no specific studies of its activity against *Neisseria gonorrhoeae* have been published.

### Povidone iodine (antiseptic)

- active *in vitro* against the two target species and present in the form of an eye irrigation solution in single-dose bottle, **but** with large volumes (20 and 50ml). Furthermore, the french MA for this irrigation solution indicated in preoperative ophthalmic surgery antisepsis, mentions that this product must never be used as a eye drops and specifies a contraindication in 0-1 month-old infants.

### Rifamycin

- active *in vitro* against the two target species, **and** the french eye drops MA, indicated in the curative treatment of conjunctivitis, keratitis and corneal ulcers, does not specify any contraindications for newborn infants ;
- clinical experience of this prophylactic use deemed satisfactory by the concerned teams ;
- no safety concerns in the context of a single topical administration ;

- **but** the eye drops is available in France only in multi-dose form.  
Considering this analysis and based on expert opinions, the rifamycin-based eye drops solution appears to be the best alternative for the prophylaxis of neonatal conjunctival infections (off-MA prophylaxis recommendations).

Although no administration schedule has demonstrated its efficacy through trials conducted in accordance with current assessment standards, most maternity unit teams use the posology of 1 drop in each of the infant's eyes at birth. Considering the pharmacokinetic-pharmacodynamic properties of rifamycin and in light of the volume administered per drop, it is recommended to instil 1 drop of rifamycin-based eye drops solution to each of the infant's eyes at birth.

## Recommendations

There are no general data available upon which to base recommendations for implementing systematic neonatal conjunctival antibiotic prophylaxis.

**As a precautionary measure, neonatal conjunctival antibiotic prophylaxis is recommended\* if patients have a prior history and/or presents with risk factors of Sexually Transmitted Infections.**

Non-monitored or poorly monitored pregnancies are considered to be at risk of STI.

In these situations, one drop of rifamycin-based eye drops solution should be instilled in each of the infant's eyes at birth.

Close attention should be paid to eye drops instillation. In the absence of single-dose pharmaceutical presentation, the iterative use of a single bottle for several children raises the risk of cross-transmission of microorganisms. Therefore a different bottle of eye drops for each child should be preferred.

The choice of non-systematic and targeted antibiotic ocular prophylaxis, administered to at-risk populations, should be accompanied by increased vigilance concerning newborn infants, with adapted care for persistent or severe mucopurulent conjunctivitis in children.

*\* except in case of Caesarean without premature rupture of the amniotic sac prior to surgery.*

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### Task force

The Afssaps drew up this review based on the assessments of a pluridisciplinary group of experts, chaired by S Auvin, paediatrician and president of the Afssaps Paediatrics Policy Committee (Paris), and comprised of: S Aho, medical officer of health (Dijon); JM Aïache, dosage form specialist (Clermont-Ferrand); R Alt, paediatrician (Strasbourg); Y Aujard, resuscitator - neonatologist (Paris); AG Bah, paediatrician (Le Mans); F Bavoux, pharmacovigilance physician (Paris); D Bremond-Gignac, ophthalmic paediatrician (Amiens); J Bouillie, paediatrician (Paris); JD Cavallo, microbiologist (Paris); C Francoal, neonatologist (Paris), V Goulet, Invs (Saint Maurice); R Grente, midwife (Paris); J Hajjar, medical officer of health (Valence); L Lassau, dermatologist - IST specialist (Paris); J Raymond, microbiologist (Paris), P Sednaoui, CNR<sup>4</sup> gonococcus (Paris) and A Wollner, paediatrician (Nogent sur Marne).

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The Review was validated by the Marketing Authorisation Commission of October 22nd Presided by D Vittecoq. This Update is available on the internet site: [www.afssaps.fr](http://www.afssaps.fr)

<sup>4</sup> CNR: Centre National de Référence (National reference centre)