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## RESEARCH ARTICLE

### OFTALMIA NEONATORUM

<sup>1</sup>Daniel Vasquez Valverde, <sup>2,\*</sup>Daniela Duarte Núñez, <sup>3</sup>Federico Cortés Bejarano and  
<sup>4</sup>Jasmín Quesada Campos

<sup>1</sup>General Physician in Private Practice, San José, Costa Rica

<sup>2</sup>General Physician in Private Practice, Heredia, Costa Rica

<sup>3,4</sup>General Physician, Ophthalmology Resident, Hospital México, Costa Rica

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#### ABSTRACT

Ophthalmia neonatorum (ON), is a broad term that includes all forms of acute and mucopurulent eye infection in the first four weeks of life and is usually acquired by the newborn during passage through the infected birth canal. The spectrum of infectious pathogens that cause neonatal conjunctivitis differs in several parts of the world, due to differences in prenatal maternal care and use of prophylactic treatment to prevent infections in the pregnant mother and the newborn. The most common infectious causes of ON include *Chlamydia trachomatis*, *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Neisseria gonorrhoeae*, other gram-negative bacteria and the herpes simplex virus; Chlamydia and Neisseria being the most common pathogens. Fortunately, in most cases, laboratory studies can identify the causative organism and, unlike other forms of conjunctivitis, this perinatal eye infection must be treated with systemic antibiotics to prevent systemic colonization of the organism. ON remains an important cause of eye morbidity, blindness and even death in underdeveloped countries. Routine prophylaxis with 1% silver nitrate solution has been discontinued in many developed countries for fear of the development of chemical conjunctivitis. Currently the recommended prophylaxis is 1cm of topical erythromycin at 0.5% ointment or 1% tetracycline in all newborns during the first hour of life.

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## INTRODUCTION

Ophthalmia Neonatorum (ON), also known as neonatal conjunctivitis, is a broad term that includes all forms of acute and mucopurulent infection of the eyes in the first four weeks of life, although it is mainly caused by bacteria it may also be due to viruses and chemical agents (Singh, 2018; Wagner, 2007; Nelson, 2016; American Academy of Ophthalmology, 2016). ON is acquired mainly during vaginal delivery, with the two most common etiologic agents being *Neisseria gonorrhoeae* (*N.gonorrhoeae*) and *Chlamydia trachomatis* (*C. trachomatis*) (Zuppa et al., 2011; Nelson, 2016; Churchward, 2017). It is the most common infection of any type in newborns, affecting up to 12% of them (Bowling, 2016) Prophylaxis reports date back from 1881 by Credé, which consisted of instilling a drop of silver nitrate solution in each eye at birth (Zloto et al., 2016). Prophylactic management is currently based on the use of tetracyclines or erythromycin in ointment (<https://doi.org/10.1053/j.spid.2005.06.006>; <https://doi.org/10.1542/pir.31-5-196>).

**Epidemiology:** Globally, the incidence of ON is highest in areas with high rates of sexually transmitted diseases (STDs) and poor medical care. The prevalence varies from 0.1% in highly developed countries with effective prenatal and perinatal care to 10-12% in areas such as East Africa (American Academy of Ophthalmology. 2016; Zloto, 2016). The epidemiology of ON changed when the silver nitrate solution was introduced in 1800, this simple treatment resulted in a dramatic reduction in the incidence of ON due to *N gonorrhoeae* from 10% to 0.3% (9). *C trachomatis* infections are currently the most common bacterial cause of ON in newborns, accounting for up to 40% of cases. *Streptococcus pneumoniae* and non-typeable *Haemophilus influenzae* both have been estimated to account for 30-50% of cases, while *N gonorrhoeae* infections account for less than 1% in the developed world (Singh, 2018)

**Etiology:** The causes of ON can be divided into two types, aseptic and septic. The aseptic type (chemical conjunctivitis) is generally secondary to the instillation of silver nitrate drops, or the use of prophylactic agents such as erythromycin or tetracycline (Matejcek, 2013).

\*Corresponding author: Daniela Duarte Núñez,  
General Physician in Private Practice, Heredia, Costa Rica.

The incidence of ON due to *C trachomatis* in the United States is 8.2 / 1,000 live births, compared to ON cause by *N gonorrhoeae* which has an incidence of 0.3 / 1,000 live births. (Nelson, 2016) Among babies born to a mother with active untreated infection of *C trachomatis* and *N gonorrhoeae*, 30 to 50% will develop clinical ON, without the use of prophylaxis (Wagner, 2008; Hammerschlag, 2011; Mallika, 2008)

**Table 1. Causes of ophthalmia neonatorum**

Chemical	- Silver nitrate - Tetracycline
Bacterial	- Erythromycin - <i>C trachomatis</i> - <i>Neisseria gonorrhoeae</i> - <i>Haemophilus</i> species - <i>Streptococcus pneumoniae</i> - <i>Staphylococcus aureus</i> - <i>Staphylococcus epidermidis</i> - <i>Streptococcus viridans</i> - <i>Escherichia coli</i> - <i>Pseudomonas aeruginosa</i> - Others
Viral	- Adenovirus - Herpes simplex virus

Source: Matejcek, A., & Goldman, RD (2013). Treatment and prevention of ophthalmia neonatorum. Canadian family physician *Medecin de famille canadien*, 59 (11), 1187-1190 .

**Table 2. Etiology and evolution time**

Diagnosis by time of appearance	Appearance time
Chemical irritation	First days
Gonococcal	First week
Staphylococci and other bacteria	End of the first week
HSV	12 weeks
<i>Chlamydia</i>	1 - 3 weeks

**Clinical features:** Regardless of the cause, ON is characterized by chemosis of the conjunctiva, eyelid edema, and discharge that may be purulent. Therefore, any newborn who develops signs of ON requires rapid and comprehensive systemic and ocular assessment to determine the causative agent and appropriate management (<https://doi.org/10.1128/mBio.00534-17>)

- Chemical conjunctivitis: refers to a slight, self-limited irritation and redness of the conjunctiva that occurs in the first 24 hours after silver nitrate instillation. This condition improves spontaneously on the second day of life (Nelson, 2016; American Academy of Ophthalmology, 2016)
- Bacterial conjunctivitis: Any conjunctivitis that appears after 48 hours of life must be evaluated for a possible infectious cause (Nelson, 2016)

**Gonococcal ON:** The usual incubation period for *N gonorrhoeae* is two to five days. Gonococcal conjunctivitis begins with mild inflammation and bilateral serosanguineous discharge, and within the first 24 hours after initial symptoms the discharge becomes thick and purulent, with possible formation of pseudomembranes to eyelid eversion. Tense eyelid edema occurs with marked chemosis (Nelson, 2016; Woods, 2005; Richards, 2010; Perry, 2018) Gonococcal infection may be present at birth or delayed beyond five days of life due to partial suppression caused by ocular prophylaxis (Nelson, 2016).

***Chlamydia trachomatis* ON:** *C trachomatis* infections are the most common cause of bacterial conjunctivitis in neonates. (Singh, 2018) The onset of conjunctivitis generally occurs around the first week of life, with an incubation period of 5 to 14 days; although the onset may be earlier, especially in cases with premature rupture of membranes. Ocular infection is characterized by minimal to moderate discharge, mild eyelid inflammation, and hyperemia with a papillary reaction in the conjunctiva. The inflammatory process mainly involves the tarsal conjunctiva and the corneas are rarely affected. Severe cases can be accompanied by a more abundant discharge and the formation of pseudomembranes (Nelson, 2016; Woods, 2005; Richards, 2010; Perry, 2018) The infant with *C trachomatis* ON may develop infection at more than one site including the nasopharynx, rectum, and vagina. (Hammerschlag, 2011)

**Viral conjunctivitis:** It is most commonly caused by adenovirus and herpes simplex virus (HSV). They are generally characterized by watery discharge, with often unilateral affection and associated with periauricular nodes. Follicular changes (lymphocyte aggregates) are often found in the palpebral conjunctiva. Up to 50% of viral conjunctivitis cases present with lymphadenopathy. Infants with ON due to adenovirus may present with petechial hemorrhage or occasionally large subconjunctival hemorrhages (Nelson, 2016; Matejcek, 2013). Infection with HSV is usually secondary to HSV-2, generally occurring later than the infection caused by *N gonorrhoeae* or *C trachomatis* which frequently presents in the second week of life. (American Academy of Ophthalmology, 2016) Neonates with generalized herpetic infection usually present with keratoconjunctivitis. Vesicles around the eye and corneal disease are also common. (Mallika, 2008)

**Clinical complications:** ON has a risk of up to 16% corneal scarring and blindness if not treated properly (Perry) In gonococcal ON, if adequate treatment is delayed, the infection may spread into the deeper layers of the conjunctiva and cornea. Complications include: corneal perforation and ulceration, iridocyclitis, anterior synechiae, and rarely panophthalmitis (Nelson, 2016)

**Diagnosis:** ON diagnosis is essentially clinical, by observing signs and symptoms. Clinical differentiation between several types of neonatal conjunctivitis can be difficult. Therefore, laboratory diagnosis takes importance to establish the correct diagnosis and initiate the best treatment (Yip, 2008) Conjunctivitis that appears after 48 hours should be evaluated for a possible infectious etiology. A Gram stain of the purulent discharge should be performed and the material should be cultured in cases of suspected gonococcal infection. If a viral etiology is suspected, a swab with the appropriate tissue culture technique should be sent for adequate virus isolation. In *Chlamydia* conjunctivitis, the diagnosis is made by examining the Giemsa-stained epithelial cells scraped from the tarsal conjunctivae to visualize the peculiar intracytoplasmic inclusions (Nelson, 2016). PCR assays may have higher sensitivity and similar specificity in diagnosing neonatal *Chlamydia* conjunctivitis compared to conventional methods (Yip, 2008)

**Prophylaxis:** Currently, the identification of maternal gonococcal infection and its adequate treatment, have become a mainstay of prenatal care (Nelson, 2016) Until the eighties;

silver nitrate was the recommended prophylaxis for ON, however, it has fallen into disuse due to the high incidence of causing chemical conjunctivitis; It also doesn't shown to be effective against *C trachomatis* and therefore has been supplanted by both erythromycin and tetracycline, which acts against *N gonorrhoeae* and *C trachomatis* (Zuppa, 2011; American Academy of Ophthalmology, 2016). The prophylactic dose of 1 cm of topical erythromycin at 0.5% ointment or 1% tetracycline, placed in the lower conjunctival sac is recommended in all newborns during the first hour of life (Matejcek, 2013). A clinical trial of ON in Kenya showed that a 2.5% povidone-iodine solution was more effective and less toxic than erythromycin or silver nitrate ointment. Povidone-iodine is particularly useful in developing countries due to its low cost and easy application (American Academy of Ophthalmology. 2016; Grzybowski, 2018).

**Treatment:** The management of ON will be conditioned by the result of the microbiological tests and the systemic state of the newborn at the time of diagnosis. Conjunctivitis caused by *N gonorrhoeae* and *C trachomatis* requires the administration of systemic and topical antibiotics. Regardless of conjunctivitis etiology, if conjunctival secretion is present, frequent irrigation with saline solution will be recommended (Palafox, 2011)

- Chemical conjunctivitis: does not require treatment, artificial tears can alleviate the symptoms (Grzybowski, 2018)
- *C trachomatis* conjunctivitis: the classic treatment is erythromycin orally (PO) at 50mg / kg / day in four doses for 14 days, but the risk of hypertrophic pyloric stenosis has been described in infants younger than 6 weeks. There are other macrolides that could be used, such as: azithromycin PO in 20mg / kg / day in one dose for 3 days, or clarithromycin PO in 15mg / kg / day in two doses for 14 days (Grzybowski, 2018 Muthiah, 2017)
- *N gonorrhoeae* conjunctivitis: Gonococcal conjunctivitis the can be treated with ceftriaxone dose of 50mg / kg / day by intramuscular (IM) or intravenous (IV) in a single dose or up to 125mg / kg. (Palafox, 2011) Alternatively, cefotaxime could be used at a dose of 100mg / kg / day by IV, or every 12 hours when IM is administered for 7 days, or 100mg / kg in a single dose. It is important to emphasize that treatment should be extended if sepsis or involvement of other extraocular sites (meningitis, arthritis). (Nelson, 2016; Moore, 2015)
- HSV type 1 and 2 conjunctivitis: Systemic treatment with acyclovir IV 60mg / kg / day should be started in three doses for 14-21 days. If there is a corneal affection, topical treatment with acyclovir ointment will be added 5 times a day for three days. (Richards, 2010; Grzybowski, 2018) The application of topical acyclovir at 3% in ointment or Ganciclovir at 0.15% ointment four times daily for 10 days is also suggested (Muthiah, 2017)
- Conjunctivitis due to other bacteria:

Gram positive bacteria: erythromycin eye ointment three times a day for 7 days. (16) Gram negative bacteria: Tobramycin eye ointment three times a day for 7 days (Grzybowski, 2018)

## Conclusion

*C trachomatis* infection is a relatively frequent cause of ON in our setting. It may associate ocular and systemic disease if is not properly treated. Therefore, in an ON scenario, health care

providers must be aware of diagnosis importance, topical prophylaxis in all neonates, to request a series of etiological diagnostic tests and evaluate topical and/or systemic treatment depending on the microbiological test results. It has to be emphasized that primary health care workers, OB/GYN specialists, neonatologists, ophthalmologists, and other medical personnel should be educated and sensitized of the global impact of this disease. ON is one of the main causes of preventable blindness in childhood and with efforts at all levels, this can be eradicated.

**Conflict of interest:** The authors declare that there is no conflict of interest.

## Glossary of Abbreviations

**C. trachomatis:** Chlamidia trachomatis  
**HSV:** Herpes Simplex Virus  
**IM:** Intramuscular  
**IV:** Intravenous  
**N. gonorrhoeae:** Neisseria gonorrhoeae  
**OB/GYN:** Obstetrics and gynaecology  
**ON:** Ophthalmia neonatorum  
**PCR:** Polymerase chain reaction  
**PO:** Orally  
**STDs:** Sexually Transmitted Diseases

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