Review Article

# An overview of neonatal conjuctivitis

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**Abstract**

Neonatal conjunctivitis has been recognized for several centuries and it is one of the most common infections occurring in the 1st month of life and remains an important cause of ocular morbidity of great health concern especially in developing countries. This article attempts to review the current epidemiology, etiology, risk factors, pathogenesis, investigations, and treatment and offer possible preventive measures to avert this potentially crippling disease. Most epidemiological reports have focused on gonococcal and chlamydial neonatal conjunctivitis because both are associated with sexually transmitted diseases and are therefore of general public health importance. The risk of conjunctivitis in newborns depends on frequencies of maternal infections, prophylactic measures, circumstances during labor and delivery, and postdelivery exposures to microorganisms. The etiological agents implicated as causes of Neonatal conjunctivitis can be classified into chemical and infective. Laboratory studies used in the diagnosis of neonatal conjunctivitis include smears, stains, cultures, and serological tests. Current World Health Organisation (WHO) guidelines for the management of sexually transmitted infections recommend that all cases of neonatal conjunctivitis be treated for both *Neisseria gonorrhoeae* and *Chlamydia trachomatis*. Four levels of intervention can be used to prevent childhood blindness and ocular morbidity from neonatal conjunctivitis. These strategies may reduce the prevalence of sexually transmitted disease, which in turn may reduce the risk to infants of exposure to agents that cause neonatal conjunctivitis.

**Key words:** Bacteria, maternal, neonatal conjunctivitis, risk factors

## INTRODUCTION

Neonatal conjunctivitis has been recognized for several centuries though case definition differed.[1,2] Neonatal conjunctivitis was originally described in 1750 by Quellmaz.[3] It is one of the most common infections occurring in the 1st month of life and remains an important cause of ocular morbidity of great health concern. Faal[4] noted that there were an estimated one and a half million blind children in the world in 1992 and every year about half a million more became blind. In Africa between 1000 and 4000 children are blinded annually by conjunctivitis.[5]

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Neonatal conjunctivitis has been defined in various ways by different authors.[6-12] Neonatal conjunctivitis according to Kolade *et al*.[13] is defined as the inflammation of the mucus membrane lining the eyelid and covering the eyeball in a newborn within the first 28 days of life whereby Gram staining of an eye smear shows at least one polymorphonuclear leukocyte per high power field.[13] According to Klaus[7] conjunctivitis is defined as an infant aged <30 days with clinical signs of redness and swelling of the eyelids and palpebral conjunctiva, purulent eye discharge, and one or more polymorph nuclear leukocytes per oil immersion field of a Gram stain conjunctival smear.[7] The WHOs working group on neonatal conjunctivitis defined it as any conjunctivitis with discharge occurring during the first 28 days of life.[8]



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## EPIDEMIOLOGY

Neonatal conjunctivitis is a worldwide problem, and although global incidence is not known, incidences of 1–24% have been reported from various regions of the world.[7] Most epidemiological reports have focused on gonococcal and chlamydial neonatal conjunctivitis. This is because, both are associated with sexually transmitted diseases and are therefore of general public health importance. In neonatal conjunctivitis, the reservoir of infection is the pregnant woman who has either gonococcal or chlamydia infection. Neonates born to such mothers have a high risk of contracting the disease during delivery or in utero if there was prolonged rupture of amniotic membranes.[14] In the United States of America, the incidence of neonatal conjunctivitis ranges from 1% to 2% depending on the socioeconomic status of the area.[6]

A higher incidence of neonatal conjunctivitis exists in developing countries.[15] In Nairobi, Kenya the incidences of gonococcal and chlamydia neonatal conjunctivitis were 40 per 1000 and 80 per 1000 live births, respectively. More than 50% of the newborns in Nairobi had concurrent gonococcal conjunctivitis.[6] This high incidence of neonatal conjunctivitis in Kenya was attributed to high prevalence of sexually transmitted infections in pregnant mothers and lack of eye prophylaxis in neonates at birth.[6] The prevalence of gonorrhoea is high among antenatal attendees in African countries ranging from 4% to 15%.[8] A report from the Makerere Medical School, Kampala Uganda showed that 75% of the neonates studied had gonococcal neonatal conjunctivitis, although the actual incidence was not stated in the report.[16] Kenya had a higher prevalence of 23.2% in the preprophylactic era.[17] However, the prevalence reduced to 17.6% after silver nitrate, 15.2% after erythromycin, and 13.3% after povidone iodine prophylaxes were introduced.

In Nigeria, a survey of neonatal conjunctivitis in Benin city with emphasis on gonococcal neonatal conjunctivitis showed an incidence of 8.9 per 1000 live births.[18] A similar study from Zaria by Ugbode[14] showed a prevalence of 2.7%. Another study from Ilorin by Kolade *et al*.[14] reported a prevalence of 13.5%.

## THE STRUCTURE AND FUNCTION OF THE EYE

Anatomically and functionally, the eye [Figure 1] is the organ of sight, a hollow globe filled with fluid (humor). The outer layer comprising the sclera and cornea is fibrous and protective. The middle layer composed of the choroids,

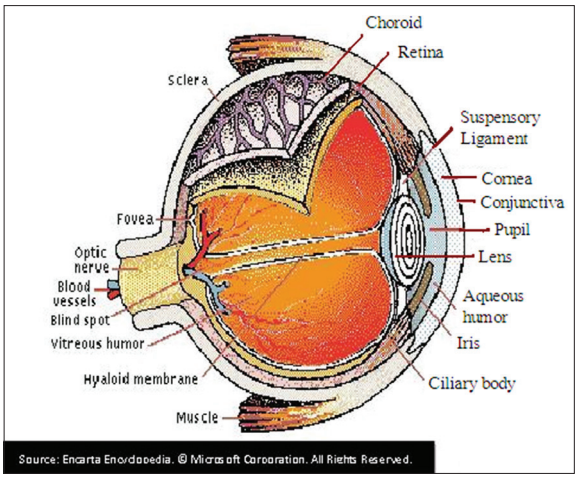


**Figure 1:** Structure of the eye as adopted from Encarta Encyclopaedia

ciliary body, and iris is vascular while the innermost layer (the retina) is nervous. The fluid in the eye is divided by the lens into vitreous humor (behind the lens) and the aqueous humor (in front of the lens).[1] The lens itself is flexible and suspended by ligaments which allow it to change shape so as to focus light on the retina which is composed of sensory neurones.[1]

The conjunctiva is a thin layer of mucous membrane which lines the eyelids and is reflected on the eyeball to cover the anterior aspect of that organ until, at the limbus, where it becomes continuous with the superficial layer of the cornea. The conjunctiva has three divisions: The palpebral/tarsal conjunctiva, which covers the posterior surface of the eyelids, the ocular/bulbal conjunctiva covering the anterior portion of the eyeball, and the fornix, the transitional portion forming a fold between the eye lid and the eyeball.[19]

The bulbar conjunctiva is thin and transparent, covers the anterior surface of the eyeball and is loosely attached to the sclera by a connective tissue, the episclera, except near the limbus where it becomes firmly adherent. Near the inner canthus, it forms a crescentic fold called the plicasemilunaris (representing the 3rd eyelid in lower vertebrates).[19] The conjunctiva of the fornix constitutes a loose fold, ensuring freedom of movement to the eyeball. Its epithelium, unlike the bulbal conjunctiva, contains three layers of cells. It is richly supplied with blood vessels. The ducts of lacrimal glands open onto it.[19]

Mechanical factors such as blinking of the eyes lead to irrigation of the eyes by tears which protect the conjunctiva from physical trauma and also reduce the duration of contact with infecting or irritating agents. The tear fluid is endowed with antibacterial properties like lysozymes and immunoglobulin A (IgA). Specific

antibodies are produced and may be detected in the tears, but their concentration is not known to be related to the outcome of conjunctivitis.

The conjunctiva of a neonate is sterile at birth but soon becomes colonized by various microorganisms that may either be pathogenic or nonpathogenic.[20] The conjunctiva is prone to infection not only because there are low levels of antibacterial agents and proteins like lysosomes and IgA and G, but also because the tear film and flow are only just beginning to develop.[17,21] Contamination of the baby's eyes with microorganisms from the mothers' genital tract or from the hands of birth attendants serves as a mode of acquiring neonatal conjunctivitis.[22]

## ETIOLOGY

The etiological agents implicated as causes of neonatal conjunctivitis can be classified into chemical and infective. The infective agents include viruses, fungi, and bacteria.[23] Bacterial agents implicated in ophthalmia neonatorum include *Neisseria gonorrhoeae* and *Chlamydia trachomatis*.[24,25] Other major causative bacterial agents includes *Staphylococcus aureus*, *Streptococcus pneumoniae, Streptococcus pyogenes, Haemophilus influenza,* and *Pseudomonas aeruginosa*.[26] In a study by Jones and Barbara,[27] *Mycoplasma hominis* was isolated from 8 out of 250 clinically infected eyes of newborn infants.[27] Robert,[28] have reported an outbreak of adenoviral conjunctivitis in a neonatal intensive care unit affecting seven premature infants who 4–7 days earlier had undergone examination for retinopathy of prematurity. Most infants acquire the herpes simplex infection during the birth process.[13] Fungi such as *Candida albican* have been reported to cause conjunctivitis in the neonatal period.[6] The conjunctivitis is usually part of an Endophthalmitis resulting from candidemia and is now well recognized especially in very low birth weight preterm neonates.[14]

Aseptic neonatal conjunctivitis is most often a chemical conjunctivitis that results from a reaction to the prophylactic agent instilled into the eye at birth to prevent bacterial ophthalmia neonatorum.[10] It is most commonly induced by silver nitrate solution which was found to be an irritant to the conjunctiva.[2,7] It has been reported to occur in 10–00% of treated neonates during the first 24 h of life and presents as a mildly purulent conjunctivitis that usually resolves within 48 h.[10] Other topical prophylactic agents used such as silver acetate and quaternary ammonium compound like benzethonium chloride, have not been studied extensively. Recently, povidone iodine 2.5% has been used and has not been documented to produce irritation.[29] In some cases, etiology of neonatal conjunctivitis remains obscure.[23,30] Several studies have documented cases of clinical conjunctivitis, with no organisms isolated. In a study by Prentice *et al*.,[31] 53.5% cases with conjunctivitis had no microorganism isolated and they proposed chemical irritation and/or unidentified microbial agents either bacterial or viral as possible causes.

## PATHOGENESIS

The pathogenesis of gonococcal and chlamydia ocular infections in the newborn are well documented but that due to other causes is still obscure.[7] Neonates acquire the gonococcus either in utero, during delivery or postnatally from medical personnel, contaminated objects in the delivery room or nursery or other individuals in the family or by autoinoculation from other infected sites.[32] The organism also known to colonize other systems leading to septicaemia in the neonate. The association of amniotic infection syndrome and recovery of gonococci in the orogastric aspirates has been described by Blank in 1959.[33]

Recovery of gonococci from orogastric aspirates of the neonate reflects contamination of the upper gastrointestinal tract, upper respiratory tract, and probably the lower respiratory tract. There is good reason to believe that this can cause infection in the neonates.

The involvement of the cornea can be severe and first appears as a diffuse corneal edema which gives the cornea a hazy appearance while opacities appear around the corneoscleral junction.[8] When new blood vessels invade the cornea scarring may result, ulceration and perforation of the globe may ensue. This occurs in untreated cases around the 3rd week. The gonococcus which is a Gram-negative intracellular diplococcus exhibits four morphologic types of colonies.[18] Only 1 and 2 appear to be virulent and possess pili which attach to epithelial cells and help to resist phagocytosis.[34] Gonococci contain several plasmids (molecular weight 4.5 × 10) which carry the gene for B-lactamase production.[34] These make the gonococci resistant to penicillins. These plasmids are transmissible among the gonococci and are acquired from *Haemophilus* or other Gram-negative organisms.[34] Gonococci attack mucous membranes of the eye and genital tract, producing within 1 and 3 days acute suppuration that may lead to tissue invasion by polymorph nuclear leucocytes. This may result in chronic inflammation and fibrosis.[34] gonococcal bacteremia leads to skin lesions especially hemorrhagic papules and pustules, arthritis, tenosynovitis, especially of the knees, ankles, and wrists. Other lesions include proctitis, pharyngitis, myopericarditis, and endocarditis.[35] Lasting immunity does not seem to develop in the course

of gonococcal infections, although IgA antibodies occur on mucous membranes.[34] Reinfection is a common occurrence.

The pathogenesis of chlamydial infections has been studied in detail by several workers.[8,34,36] Chlamydial neonatal conjunctivitis is caused by *C. trachomatis* serotypes D to K, which are the same serotypes that cause genital infections in man.[34] It is a Gram-negative *Bacillus* with an incubation period of 5–14 days.[8] The fact that the neonate acquires the organism from the maternal cervix during delivery has been substantiated by various workers.[37,38] Rees *et al.* studied 103 babies with conjunctivitis, 33 of whom had a chlamydia infection.[37] About 66% of their mothers had chlamydia isolated from their cervix.[37] Transmission rates from mother to baby has been calculated in various studies and ranged from 28% in studies by Heggie *et al.*[38]

## PERIOD OF OUTSET

Chemical conjunctivitis secondary to silver nitrate solution application usually occurs on the 1st day of life, disappearing spontaneously within 2–4 days.[6] Meconium or other irritants have similar effects on the conjunctiva. Gonococcal neonatal conjunctivitis tends to occur 3–5 days after birth, but can present later especially if topical prophylaxis has been used.[6] A study by Hansfield *et al.* reported that the incubation period ranged from 1 to 21 days, and purulent discharge occurred in 81% and was mostly bilateral.[33] In another study at the Liverpool Royal Imfirmary, the onset of eye discharge was 1–8 days.[37] while in one case report from Lagos, Nigeria, the baby presented with foul smelling bilateral and purulent eye discharge at birth.[39]

Chlamydia conjunctivitis usually has a late onset than gonococcal conjunctivitis. Incubation period of 5–14 days after delivery[6] was reported with approximately 50% being bilateral.[6] The Incubation period for nongonococcal nonchlamydial conjunctivitis is longer.[40] Herpetic conjunctivitis usually occurs during a first 2 weeks after birth.

## CLINICAL FEATURES

Significant overlap in clinical presentations of neonatal conjunctivitis may be present.[6] The clinical features of neonatal conjunctivitis may range from mild stickiness to conjunctival hyperemia, purulent eye discharge, and significance eyelid edema.[6] The severity of presentation depends on the infective organism.[22] Sandstorm[40] proposed that there are three clinical presentations that may suggest the etiology of neonatal conjunctivitis. These include purulent eye discharge, edema of the eyelid, and hyperemia of the conjunctiva. Noninfective causes may produce hyperemia and trauma may cause swelling of the eyelid making the diagnosis difficult in these circumstances.[40]

Gonococcal neonatal conjunctivitis tends to be severer than other causes; there is a classic presentation of purulent conjunctivitis which is usually bilateral.[6] There may be corneal involvement including diffuse epithelial edema and ulceration that may progress to perforation of the cornea and Endophthalmitis.[6] The patient may also have systemic manifestations such as; rhinitis, stomatitis arthritis, meningitis, anorectal infection, and septicaemia.[6] The clinical features of chlamydial neonatal conjunctivitis may range from mild hyperemia with scanty mucoid discharge to eye swelling, chemosis, and pseudomembrane formation.[6] Blindness though rare and slower in onset than in gonococcal neonatal conjunctivitis is due to eyelid scarring and pannus formation.[6] Follicular reaction does not occur because newborns have no lymphoid tissue in the conjunctiva.[6] Chlamydial neonatal conjunctivitis may also be associated with extraocular involvement such as pneumonitis, otitis media, pharyngeal, and rectal colonization.[6] Herpes simplex keratoconjunctivitis usually present in infants with generalized herpes simplex infection.[2] Serious systemic complications such as encephalitis may occur due to poor immunologic response.[6]

## LABORATORY DIAGNOSIS

Laboratory studies used in the diagnosis of neonatal conjunctivitis include smears, stains, cultures, and serological tests.[41] Growth of commensal organisms can be prevented by the use of selective culture media which inhibit the growth of commensals but support the growth of pathogens suspected of causing the infection.[42] Contaminants or commensals can also be differentiated from pathogenic organisms by morphological appearance, biochemical tests, and enzymes production.[42] Criteria for the identification of the organisms include: (a) Macroscopic appearance (b) microscopic appearance involving the Gram staining properties which can be Gram-positive or negative (c) culture methods and (d) biochemical tests including catalase, coagulase, urease, citrate, triple sugar inhibition, and sugar fermentation tests.[42] A smear of specimen for microscopic study is prepared by rolling a small quantity of the specimen material across a glass slide.

Serological tests are used for detection of immunological response to infective agents.[41] For most pathogens, detection of IgM antibodies or a fourfold increase in the patient's antibody titre is diagnostic of current infection.[41] Other techniques include direct fluorescent

antibody.[43] and antigen immunochromatographic test.[44] The immunochromatographic test has been found to have an acceptable sensitivity (83.5%) and good specificity (98.9%) compared to molecular testing.[44]

Nucleic acid amplification test (NAAT) is currently the standard method for detection of chlamydia where facilities exist.[44] The test finds the genetic material (DNA) of chlamydia and is the most sensitive test available. It is very accurate and unlikely to have false positive result. Polymerase chain reaction is an example of this test (NAAT). The advantage of this test is that it is generally more sensitive and specific than conventional culture and can, therefore, identify positive specimens.[44]

## TREATMENT

Current WHO guidelines for the management of sexually transmitted infections recommend that all cases of neonatal conjunctivitis be treated for both *N. gonorrhoeae* and *C. trachomatis*.[45]

### Neonatal conjunctivitis due to *Neisseria gonorrhoeae*

Treatment of gonococcal conjunctivitis consists of intravenous Penicillin G 100,000 units/kg/day for 1 week. *N. gonorrhoeae* isolates are resistant to penicillin in many areas. Across Africa, rates of penicillinase producing *N. Gonorrhoeae* range from 18% to 57% and other parts of the world (50–60%).[46] Hence, a third generation cephalosporin drug should be used for 7 days in areas where penicillinase producing strains are endemic. A single dose of ceftriaxone 50 mg/kg as a single dose (maximum 125 mg) is highly effective and recommended by WHO guidelines.[47,48] Alternative medications include spectinomycin 25 mg/kg (maximum 75 mg) as single intramuscular dose and kanamycin 25 mg/kg (maximum 75 mg.[49] Infected mothers should also be treated with single dose of ceftriaxone (25–50 mg/kg). The infant's eyes should also be frequently irrigated with normal saline to eliminate the discharge.

### Neonatal conjunctivitis due to *Chlamydia trachomatis*

WHO and American Acadamy of Paeditrics recommendations include oral erythromycin 50 mg/kg/day, in 4 divided doses for 14 days.[50] Topical erythromycin or tetracycline can be used as an adjunt therapy. The advantages of oral erythromycin include eradication of nasopharyngeal carriers, treatment of associated pneumonitis and also being more effective than topical in preventing relapse of conjunctivitis. Infected partners should receive oral doxycycline 100 mg twice daily for 7 days or azithromycin 1 g orally as a single dose.[45]

### Nongonococcal nonchlamydial neonatal conjunctivitis

Preliminary presumptive treatment pending culture confirmation should be based on clinical suspicion. Therapy can be modified when results of culture and sensitivity are known. Empirical treatment should include erythromycin ointment and intravenous or intramuscular third generation cephalosporin.[51] Erythromycin or bacitracin ointment can be used for conjunctivitis due to Gram-positive organisms while gentamicin or tobramycin drops are used for Gram-negative bacterial organisms.[51]

### Neonatal conjunctivitis due to *Herpes simplex and chemical conjuctivitis*

Herpetic neonatal conjunctivitis should be treated with systemic acyclovir to reduce the chance of a systemic infection. The effective dose is 30 mg/kg/day intravenously in 3 divided doses.[52] The duration of therapy ranges from 14 to 21 days. Neonates with herpes simplex viral keratitis should receive a topical ophthalmic drug like 1% trifluridine drops or 3% vidarabine.[52]

Chemical conjunctivitis usually requires no treatment; however lubrication with artificial tear preparation may ease discomfort.[6]

## PREVENTION

Four levels of intervention can be used to prevent childhood blindness and ocular morbidity from neonatal conjunctivitis.[53] The first involves the prevention of sexually transmitted diseases. The emergence of infection with human immunodeficiency virus has led to health promotion programs concerned with sexual behavior (promoting monogamous relationships and use of barrier contraceptives). These strategies may reduce the prevalence of sexually transmitted disease, which in turn may reduce the risk to infants of exposure to agents that cause neonatal conjunctivitis.[53]

The second approach consists of antenatal screening. Neonatal conjunctivitis can be prevented by screening pregnant women for genital infection, particularly those at high risk for the disease. Women with culture positive infections and their partners require adequate systemic treatment with follow-up throughout pregnancy and delivery.[53]

The third approach is ocular prophylaxis at birth, which is simple and inexpensive.[53] It consists of cleaning an infant's eyelids with a dry swab as soon after birth as possible and then instilling a safe, available, and affordable antimicrobial agent.[53] Under the British Columbia Health

Act Communicable Disease Regulation (1995), a physician, midwife, or other qualified person assisting at birth of a baby must within 1 h of birth treat the eyes of the baby with a prophylactic solution of 1% tetracycline hydrochloride, 0.5% erythromycin, or 1% silver nitrate dispensed in single-use containers.[54-56] Isenberg *et al*.[5] reported on the use of a 2.5% solution of povidone-iodine as prophylaxis against neonatal conjunctivitis. It has *in vitro* activity against a wide spectrum of bacteria, including chlamydia, and some viruses. Its use as a topical ocular antimicrobial agent appears promising particularly in developing countries.[5]

For very premature babies whose lids are fused at the time of birth, apply the prophylactic agent without separating the eyelids.[57] when 1% tetracycline or 0.5% erythromycin is used, a line of ointment 1–2 cm long is placed in each lower conjunctival sac, if possible covering the whole lower conjunctival area. Gently massage the closed eyelids to help spread the solution to all areas of the conjunctiva.[55] when 1% silver nitrate is used, two drops of solution are placed in each lower conjunctival sac, a single ampoule being used for each eye. Primary caregivers need to be informed that transient chemical conjunctivitis may occur.[55] After 1 min, any excess ointment or drops should be gently wiped from the eyelids and surrounding skin with sterile cotton.[56] the eyes should not be irrigated after instillation of a prophylactic agent.[55,58]

Finally, early diagnosis and adequate treatment of neonatal conjunctivitis can prevent corneal ulceration and blindness. The WHO vision 2020 "The Right to Sight, Global Initiative for the Elimination of avoidable Blindness" is highly committed to the control of blindness in children.[25] In order to eliminate childhood blindness due to neonatal conjunctivitis, an interdisciplinary approach is required involving gynecologists, neonatologists, ophthalmologists, and most important all primary health care workers.[53] Those at the greatest risk are infants born to mothers from areas with a high prevalence of sexually transmitted disease and limited availability of topical ocular antimicrobial agents.[53] All primary health care workers should be educated about the cause, prevention, and treatment of neonatal conjunctivitis. With increased awareness of the disease, ready availability and widespread use of a suitable prophylactic agent and appropriate treatment when needed, neonatal conjunctivitis will not lead to blindness.[53]

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