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Ophthalmia Neonatorum

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Abstract

Ophthalmia neonatorum, inflammation of the conjunctiva with discharge manifesting within the first 28 days of life, is acquired by the neonate during passage through the infected birth canal. This condition also known as neonatal conjunctivitis can result in visually disabling complications [1]. The spectrum of infectious pathogens which cause neonatal conjunctivitis differs in various parts of the world, depending upon the relative prevalence of prenatal maternal care and the use of prophylactic treatment to prevent infections in the pregnant mother and the newborn infant [3].

The common infectious causes of ophthalmia neonatorum include *Chlamydia trachomatis, Staphylococcus aureus, Staphylococcus epidermis, Escherichia coli, Neisseria gonorrhea,* other gram-negative bacteria, and Herpes Simplex virus [2,6,8]. Data support a high index of suspicion based on history and clinical presentation, various diagnostic techniques and modes of antimicrobial therapy as all contributory to reducing the occurrence of neonatal conjunctivitis.

Keywords: Neonatal conjunctivitis; Chlamydia trachomatis; Staphylococcus aureus; Staphylococcus epidermis; Neisseria gonorrhea; Escherichia coli; Herpes Simplex virus

Epidemiological Features

The beginning of the twentieth century saw the advent of screening pregnant females for sexually transmitted diseases (STDs) prior to the widespread use of prophylactic eye drops. This period was marked by the prevalence of neonatal conjunctivitis which was much higher than today. The World Health Organization (WHO) reports that in 1986, the prevalence rate of neonatal conjunctivitis as the cause of vision loss in children in European institutions was 20%-79% [16]. Infectious neonatal conjunctivitis occurs in 1-2% of all births, in the United States today [17]. Unfortunately, in underdeveloped countries, neonatal conjunctivitis remains a major problem due to inadequate maternal care and the lack of widespread use of prophylactic treatment to prevent infections immediately following birth [18]. Statistics reveals that in developed countries.

Overall, infectious conjunctivitis occurs in 12% of neonates, and 23% of neonates are afflicted with this condition in developing nations [10,19]. Laga et al. report that in a Nairobi hospital wherein no ocular prophylaxis against ophthalmia neonatorum was used, the incidence of ophthalmia neonatorum was 23.2 per 100 live births, and incidences of gonococcal and chlamydial ophthalmia were 3.6 and 8.1 per 100 live births, respectively. The infectious agents responsible, in order of frequency, were *C. trachomatis* (31%), *N gonorrhea* (12%), and both (3%) in 181 cases of neonatal conjunctivitis. Data encompassing 67 neonates exposed to maternal gonococcal infection and 201 exposed to maternal chlamydial infection showed rates of transmission to the eye of 42% and 31%, respectively [10].

De Schryver et. al (1990) reported that 1-5% of newborns globally are at risk of gonococcal ophthalmia neonatorum [18]. *C.trachomatis* has replaced *N.gonorrhea* as the most important single etiology even in developing countries, causing up to 32% of all cases [20,29]. The transmission rate from an infected mother to the newborn has been reported to range from 30-45% for *N.gonorrhea* and 30% for *C.trachomatis* [7,20]. Chlamydial infections are the most common STDs in the United States [35,36] It is also the most frequently identifiable infectious cause of ophthalmia neonatorum, with an incidence of 8.2/1000 births [12] . Wu et al. [14] reported that in China, it has been detected in 51.2% of Chinese infants [14]. *Staphylococcus aureus* is the most commonly detected organism in countries like Argentina (27.6%) [4] and in Hong Kong (36%) [2]. The differences in results may be due to epidemiological variations in different countries and also be a reflection of the spectrum of sexually transmitted diseases prevalent in these respective communities [9] (Table 1).

Pathophysiology

Vertical transmission from the mother is the route of transmission to the affected newborn. Both parents, however, should be screened for STD infection [7,12]. The ocular surface is well-equipped with unique

Location	Authors	Year	Most common pathogen
Argentina	Di Bartolomeo,Higa, Janer,et.al.[4]	2005	*S.aureus*
China	Wu,Yang,Liu[14]	2003	*Chlamydia trachomatis*
Germany	Schaller, Miño de Kaspar, Schriever, Klauss[69]	1997	*Chlamydia trachomatis*
Hong Kong	Chang, Cheng, Kwong[2]	2006	*S.aureus*
Kenya	Laga, Plummer, Nzanze, Namaara,Brunham, Ndinya-Achola,Maitha,Ronald, D'Costa, Bhullar, et.al.[10]	1986	*Chlamydia trachomatis*
Thailand	Sergiwa,Pratt,Eren,Sunona, Hart [70]	1993	*Chlamydia trachomatis, S.aureus*
United Arab Emirates	Nsanze, Dawodu ,Usmani , Sabarinathan, Varady[71]	1996	*S.aureus*
United States	O'Hara[12]	1993	*Chlamydia trachomatis*

Table 1: Vertically-transmitted neonatal conjunctivitis.

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anatomic and functional features that prevent bacterial infection in the healthy eye, both in infants and adults. Immunoglobulins, lysozyme, complement, and multiple antibacterial enzymes are found in tears. The tear film that is continuously being replenished creates an environment that makes it very difficult for bacteria to thrive. Basically, it is through successful invasion that *N.gonorrhea* overcomes intact epithelial barriers [62]. Fortunately, most bacteria rely on a break in the barrier function. Bacterial exotoxins such as those found in *Streptococcus* and *Staphylococcus* species can induce necrosis. While most pathogens are cleared from the site of infection in the acute phase; some strains can persist. *C. trachomatis* for example survives and persists within intracellular phagosomes [62].

C. trachomatis serotyping is based on immunogenic epitope analysis of the major outer membrane protein (MOMP), and it differentiates 18 serovars. Among these, serovars A to C are associated with trachoma; serovars D to K are common in adult urogenital and ocular infections, in both adults and neonates alike. Although these facts have long been established, it was only recently that serovar E was determined to be the most frequently detected serovar (71%) in neonatal ocular samples in a Buenos Aires community [66].

Clinical Picture

The signs and symptoms of ophthalmia neonatorum are similar for most of the infectious agents and they include injection of the conjunctiva associated with periorbital edema and purulent discharge [5]. Though a self-limiting disease, it has the potential to have serious consequences including severe keratopathy and serious systemic involvement if left untreated [13,15]. Early detection and specific treatment are therefore of utmost importance to prevent the complications of these infants. This type of conjunctivitis is inflammation of the conjunctiva with discharge, typically manifesting within the first month of life. Because neonatal conjunctivitis may result from varied causes, it is necessary to make an accurate diagnosis in order to begin appropriate treatment. Proper treatment directed at each specific cause can help minimize complications and loss of vision.

Neonatal conjunctivitis may be infectious, caused by bacterial, chlamydial, viral, or fungal pathogens, or can be inflammatory and non-infectious, caused by prophylactic silver nitrate solution. The silver nitrate as a prophylactic agent does cause chemical conjunctivitis, especially when the concentration of the chemical becomes toxic in tropical countries [5]. An important differential diagnosis includes preseptal cellulitis, but empiric treatment for bacterial pathogens is likely to be effective for cellulitis as well.

Despite their immature immune system, neonates are infrequently infected during their passage through the birth canal. Traumatic delivery or premature rupture of maternal membranes may increase the risk of infection. The presence of active cervical or vaginal maternal infection markedly increases the risk of neonatal conjunctivitis. Cervical infection with gonorrhea results in positive cultures from neonatal conjunctiva in 30-50% of cases [20]. Cervical infection with Chlamydia carries a risk to the neonate to 18-50%, and active vaginal herpes infection carries a low risk of transmission to newborns, but studies are limited [21-24]. However, the risk of transmission in cases of recently acquired genital herpes may be as high as 48% [25] .The differences may be due to epidemiological variations in different countries and also be a reflection of the spectrum of sexually transmitted diseases prevalent in these communities [23]. Pseudomembranes or true membranes may occur and lead to scarring if untreated [39,40]. Untreated disease can lead to chronic infection lasting many months [41].Vision loss is usually due to eyelid scarring and consequent corneal pannus. Systemic development of Chlamydial pneumonitis, otitis, and pharyngeal involvement has been reported [42]. A majority of infants with chlamydial conjunctivitis develop chlamydial pneumonitis: approximately 50% of infants with chlamydial pneumonitis have concurrent conjunctivitis or a recent history of conjunctivitis [63].

Other bacterial causes of neonatal conjunctivitis include Hemophilus, Staphylococcal and Streptococcal species and Neisseria gonorrhea. Often described as "hyperacute conjunctivitis," the incubation period for Neisseria gonorrhea may be as short as 1-7 days [37,38]. Infection is more often bilateral and signs are more severe than nongonococcal infections. Early serosanguinous exudate may be replaced by copious mucopurulent discharge within 24 hours and membranes may be seen. Marked eyelid swelling, injection and swelling of the conjunctiva are common and corneal involvement is seen in 16% of cases [62] (Figure1). Untreated infections can rapidly progress to corneal ulceration, perforation and endophthalmitis. Infected infants may also have other localized gonococcal infections such as rhinitis and proctitis. A disseminated gonococcal infection with arthritis, meningitis, pneumonia and sepsis that may lead to death of an infant is fortunately, very rare [62].

There have been very few publications about hospital-acquired conjunctivitis (Table 2). In a neonatal intensive care unit (NICU), the most common isolated in patients with conjunctivitiscoagulase-negative staphylococci and *Klebsiella* species [28]. Tarabishy et al. [63] found 30% of children developed bacterial conjunctivitis after two days of hospitalization at the Cleveland Clinic harbored gram-organisms. The rate of methicillin resistance in patients with *Staphylococcus* species-conjunctivitis was noted to be higher in those hospitalized more than two days than those *Staphylococcus* species who were hospitalized for less than two days. This leads one to surmise that among NICU inpatients, the pathogens causing conjunctivitis are not the usual suspects in the outpatient setting [63] (Table2).

Diagnostic Modalities

Proper and definitive diagnosis of the cause of neonatal conjunctivitis depends on laboratory identification of the causative organism. The

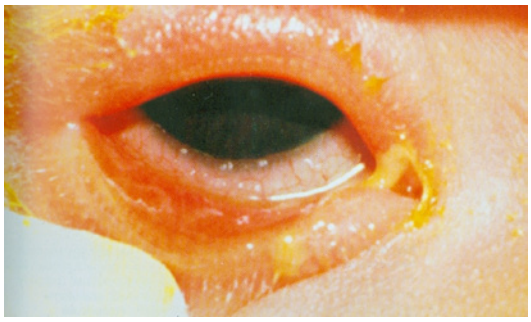

Figure 1: Gonococcal conjunctivitis of the newborn. This is acquired during passage through the birth canal and occurs a few days after birth. A mucopurulent discharge is usually present. Gram staining reveals intraepithelial Gram-negative diplococci. Aggressive treatment with systemic and topical antibiotics is indicated, as severe corneal ulceration can occur.

Location	Authors	Year	Most common pathogen
Finland	Sarvikivi,Karki,Lyytikäinen,the Finnish NICU Prevalence Study Group[72]	2010	*S.agalactiae*(early onset);*S. aureus,coagulase-negative staphylococci,E.coli*(late onset)
Israel	Borer,Riven,Golan,Odes,Zmora,Raz,Melamed, Plakht,Peled[73]	2010	*coagulase-negative staphylococci*

Table 2: Hospital-acquired neonatal conjunctivitis.

AUTHOR and DATE	METHODS	PARTICIPANTS and SETTING	INTERVENTIONS	OUTCOMES	SUMMARY OF FINDINGS

Table 3: (Characteristics of included studies) from the article: "A meta-analysis of the efficacy of ocular prophylactic agents used for the prevention of gonococcal and chlamydial ophthalmia neonatorum."

speed of progression characteristic of N.gonorrhea conjunctivitis makes it imperative to perform smears, as it may be possible to identify gram-negative diplococci and initiate proper treatment within hours. Gram staining of conjunctival swabs may be positive in up to 100% of gonococcal infections [48,49]. Giemsa staining may be helpful in identifying types of inflammatory cells, but is unlikely to provide definitive diagnostic information [50,51]. Other non-culture methods such as direct fluorescent antibody testing, enzyme immunoassays and nucleic acid testing (NAT) may allow early detection of Chlamydia within hours rather than several days, as required for culture methods [52].

These tests are not widely available and not FDA-approved for use on conjunctival samples [53].Traditional culture methods include the use of appropriate media (blood agar, chocolate agar or Thayer-Martin media and thioglycolate broth). Because Chlamydia is an intracellular parasite, it is necessary to grow cultures using tissue culture media and examine for the presence of intracellular inclusions [54].

Management

Prophylactic treatment to reduce the incidence of neonatal infectious conjunctivitis began with the use of silver nitrate, proposed by Crede in 1881 [26]. Effective at inactivating gonococci by agglutination, silver nitrate caused a transient, mild conjunctival inflammation in over 90% of treated eyes, characterized by redness and tearing that resolved within 24-48 hours [27,28]. More recently, prophylactic treatment has shifted to the use of erythromycin in the United States, which is well tolerated. Povidone-iodine is increasingly used elsewhere, however [68]. A recent meta-analysis has found in their review that both erythromycin and povidone-iodine are more effective than silver nitrate in the prevention of chlamydial ophthalmia neonatorum. This finding however comes with a warning that the evidence might not be sufficient (see Table 3, permission pending).

Treatment of neonatal conjunctivitis should be initially based on the history, clinical presentation and results of smears. Later, as laboratory results become available, specific therapy can be instituted.

Given the high incidence of extra-ocular infection in neonates with Chlamydia conjunctivitis, systemic therapy is appropriate. A fourteen day course of twice-daily oral erythromycin has been reported to eliminate Chlamydial infection in 80-100% of patients. The CDC recommends dosing at 50 mg/kg/day in four divided doses for two weeks [55]. Failure to respond to this course is grounds for repeating the fourteen courses before changing therapy to trimethoprim-sulfamethoxazole 0.5 ml/kg/day in two doses daily for two weeks [56]. Macrolide antibiotics such as azithromycin, clarithromycin and roxithromycin may be more effective against Chlamydial infections [57], but have not been well studied in neonatal Chlamydial conjunctivitis. The results of one study involving a limited number of patients suggest that a short course of azithromycin, 20 mg/kg/day orally, 1 dose daily for 3 days, may be effective [58].

Gonococcal conjunctivitis can be treated with ceftriaxone 50 mg/kg/day given either intramuscularly or intravenously, or as a single dose treatment of 125mg [25,35,59]. Alternative therapies include cefotaxime 100mg intramuscularly or 25 mg/kg given either intramuscularly or intravenously every 12 hours for 7 days [58,61].

Herpetic conjunctivitis can be treated with topical trifluridine 1% solution given every two hours for 14 days and should not be administered for more than 21 days because of potential corneal epithelial toxicity, blepharitis, cannicular occlusion, and allergies [47,50,67]. First-line therapy for acute superficial herpetic keratitis outside the United States employs ganciclovir ophthalmic gel, 0.15%, applied five times a day for ten days. Another study suggests using this gel five times daily until the corneal ulcer heals, then three times daily for a week [67] . Many pediatricians also use either oral acyclovir 30 mg/kg/day for 10 days or intravenous acyclovir 10 mg/kg or 500 mg/m^2 every 8 hours for 10 days [50].

The diagnosis of neonatal conjunctivitis must be made promptly to facilitate rapid initiation of effective therapy. It cannot be overemphasized how primary healthcare workers, obstetrics-gynecology specialists, neonatologists, ophthalmologists and other medical staff should be educated and made aware about the global impact of this disease. Ophthalmia neonatorum is a major preventable cause of childhood blindness and with efforts on all levels, this can be eradicated.

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