Original Report

Incidence of *Chlamydia trachomatis* and Other Potential Pathogens in Neonatal Conjunctivitis

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ABSTRACT

Objective: Ocular infection in neonatology is a permanent and important health problem. To improve primary attention, prevention, and control, the study of the potential bacterial etiology of all consecutive cases of conjunctivitis was incorporated as a regular procedure in primary care from July 1995 to December 1998.

Materials and Methods: Prof. A. Posadas Hospital (Great Buenos Aires) has an average of 4294 births per year. This report analyzes the results obtained in 332 infants (age range, 0–30 d) with conjunctivitis.Clinical conjunctivitis was diagnosed in inpatients and outpatients by the same specialized staff. Isolation and characterization of bacteria were done by conventional microbiologic methods, including specific search for *Neisseria gonorrhoeae* and *Chlamydia trachomatis*. *Chlamydia trachomatis* was studied by antigen immunodetection and polymerase chain reaction, and genotyped by restriction fragment length polymorphism.

Results: Conjunctivitis had an incidence (cases per 1000 live births) of 39.6 in 1995, 25.3 in 1996, 15.4 in 1997, and 15.2 in 1998. Microbial growth was detected in 167 (50.3%) of 332 cases. Ocular *C. trachomatis* infection was detected in 26 cases (7.83%). Five of seven isolates in tissue cultures belonged to type E and two to type G. Bacteria from respiratory ecology were the main isolates: *Haemophilus influenzae* (16.9%), *Streptococcus pneumoniae* (12.3%), and *Staphylococcus aureus* (8.7%). *Haemophilus influenzae* isolates were not serotyped and 17.2% of them were β-lactamase producers. In 15 cases both *H. influenzae* and *S. pneumoniae* were isolated together. Of *S. pneumoniae,* 4.9% were oxacillin resistant.

Conclusions: There has been a decline in the total number of cases of neonatal conjunctivitis, but the disease is still an important health problem. *Chlamydia trachomatis* also shows a decreasing profile with an incidence of (cases per 1000 live births) 4.39 in 1995, 1.85 in 1996, 1.01 in 1997, and 0.78 in 1998, and a tendency to show more incidence in spring-summer and significant accumulation of cases in babies between 7 and 9 days of age. *Haemophilus influenzae* alone (12.3%) or associated with *S. pneumoniae* (4.5%) appears as a prevalent potential bacterial pathogen. A significant accumulation of *H. influenzae* and *S. pneumoniae* cases occurs in winter. In 47.6% of cases, there was no bacterial growth. No significant seasonal differences in percentage of negative cultures or among the three-day age groups were detected. *Neisseria gonorrhoeae* was not found associated with ophthalmia neonatorum in this series.

Key Words: Chlamydia trachomatis, *conjunctivitis, neonates*

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OPHTHALMIA NEONATORUM, INCLUSION CONJUNCTIVITIS OF THE NEWBORN

Pinkeye, generically called conjunctivitis, is a relatively frequent disease in newborns in their first 30 days of life. It is usually associated with bacterial colonization, with a lower incidence of viral and rarely of fungal infections. Inflammatory or allergic reaction to several environmental inducers are an important cause of pinkeye.

According to several serial studies 15 to 50% of all cases remain negative for demonstrable infectious agents. Depending upon the associated agent, in most cases, the disease is self-limiting.

Information is not available about the incidence of *N. gonorrhoeae* and *C. trachomatis* or about the potential significance of other microorganisms in the ocular diseases in newborns in the highly populated area served by the Posadas Hospital. To record definite guidelines, laboratory diagnosis of *C. trachomatis* and *N. gonorrhoeae* and search for other common bacteria were established as standard procedure between July 1995 and December 1998. Although acute hemorrhagic conjunctivitis is also induced by viruses, it was not possible to include a systematic study of viral etiology at the time of the study.[1-3]

A variety of bacteria, mostly representative of respiratory ecology, have been found to be associated with neonatal conjunctivitis. Sandstrom et al found that *H. influenzae*, *Staphylococcus aureus*, *C. trachomatis*, *Streptococcus pneumoniae*, and Enterococci had a significant incidence, which they reported in a classic case-control study. It is remarkable then, that 42% of the patients remain negative by bacterial culture.[4]

Gigliotti et al demonstrated that *H. influenzae* (42% vs. 0%), *S. pneumoniae* (12% vs. 3%), and adenovirus (20% vs. 0%) were associated with conjunctivitis versus controls. *Staphylococcus aureus* was equally prevalent in diseased and control eyes.[5]

In another study of the bacteriology of normal and inflamed conjunctivae in the newborn, Kaivonen found that only *S. aureus* was recovered more often from purulent conjunctival exudates than from normal conjunctivae.[6] *Haemophilus aegyptius* has been identified as the causative microorganism of epidemic conjunctivitis in children from 6 months to 5 years of age.[7] Medeiros et al found *S. pneumoniae* and *H. influenzae* to be associated with an outbreak of conjunctivitis in Ribeirão Prêto, Brazil.[8] Evidence of a decline of *N. gonorrhoeae* and *C. trachomatis* endemic morbidity in Buenos Aires metropolitan area has been established.[9]

The first objective of the present study was to establish the incidence of *N. gonorrhoeae* and *C. trachomatis* in ocular infections in newborns. An attempt was made to integrate basic epidemiologic knowledge about other prevalent bacterial species associated with neonatal conjunctivitis and their drug susceptibility profiles, to update the standard guidelines for primary therapy.

MATERIALS AND METHODS

Clinical diagnosis of conjunctivitis in infants from 0 to 30 days of age was performed on inpatients and outpatients. From July 1995 to December 1998, 332 consecutive cases were diagnosed and bacterial isolation was completed. All cases were dealt with under standard approved hospital procedures; individual consent was not required for microbiologic study. Control cases were not included in this study.

During the first contact with the patient, ocular secretion samples were obtained with swabs and processed immediately at the laboratory. All these samples were studied by direct Gram examination and were cultured in blood agar, chocolate agar, and Thayer-Martin medium. Identification of isolated microorganisms was done by conventional procedures. Briefly, *H. influenzae* was isolated in agar chocolate media, supplemented with PoliViteX (bioMérieux) or IsoVitaleX (BBL), incubated at 37°C in 5 to 10% carbon dioxide atmosphere. Isolates compatible with *H. influenzae* were tested in Mueller-Hinton media (Difco Laboratories, Detroit, MI), with the addition of growth factors V, X, and XV (Difco). Strains that grew in XV in CO_2-enriched atmosphere, after a 24-hour incubation period, were identified as *H. influenzae*.[10]

An additional conjunctival sample was obtained, using the original material provided with the Chlamydiazime kit (Abbott Laboratories, Chicago, IL). *Chlamydia trachomatis* was identified by antigen detection with the enzyme-linked immunosorbent assay (ELISA), using the confirmation procedure. Polymerase chain reaction (PCR) was used to reconfirm the presence of *C. trachomatis*.[11] In seven cases, *C. trachomatis* was isolated using McCoys cell cultures to obtain preliminary information about types. Restriction fragment length polymorphism (RFLP) was performed as described by Isobe et al.[12]

The drug sensitivity profile of microorganisms was done by agar diffusion techniques and chromogenic detection of β-lactamases.[13] Distribution of cases by season and by age (groups of 3 days of age after birth) were analyzed by calculation of odd ratios with Cornfield 95% confidence limits and significance (P-value) adjusted by Mantel-Haenszel or Yates corrections.

RESULTS

The annual average of live births during the period of study (July 1995 to December 1998) was 4294 (range, 3814-4862). Conjunctivitis cases per 1000 live births were 39.6 in 1995, 25.3 in 1996, 15.4 in 1997, and 15.2 in 1999.

A microbiologic study for common organisms and *N. gonorrhoeae* was performed in 332 cases. Microbial growth was established in 174 (52.4%), and 47.6% were free from demonstrable pathogenic bacteria. Among positive cultures 149 (85.6%) were found to be monobacterial cultures, 21 (12.6%) were two bacterial species, and 5 (2.87%) yielded a polymicrobial culture. The identification and frequency of isolated species is shown in Table 1. Seasonal incidence of *H. influenzae* and *S. pneumoniae* showed a significant increase of cases in winter, but they were isolated throughout the year (Table 2). *Haemophilus influenzae* incidence did not show any significant differences between groups of neonates whose ages ranged from 0 to 3 to 28 to 30 days (Table 3). Sensitivity to cur-

Table 1. Frequency of Microorganism Isolates

Microorganism	*Frequency*	*Percentage*
Haemophilus influenzae	56	16.8
Streptococcus pneumoniae	41	12.2
Staphylococcus aureus	29	8.7
Streptococcus (α-hemolytic)	18	5.4
Corynebacteriun spp	14	4.2
Branhamella catarrhalis	9	2.7
Staphylococcus (coagulase negative)	4	1.2
Pseudomonas aeruginosa	2	0.6
Candida spp	1	0.3
Citrobacter freundii	1	0.3
Enterobacter cloacae	1	0.3
Klebsiella pneumoniae	1	0.3
Moraxella spp	1	0.3
Neisseria spp	1	0.3
Pseudomonas spp	1	0.3

rent antimicrobial agents indicated that 17.2% of *H. influenzae* were β-lactamase producers and 3.9% of *S. pneumoniae* were oxacillin resistant. In 15 cases, both *H. influenzae* and *S. pneumoniae* were present together.

Negative cultures appeared in 47.6% of the cases studied. The seasonal distribution of this important number of cases did not show any significant difference (see Table 2). The seasonal distribution of negative bacterial cases, did not show any particular accumulation. The weekly mean number of infants with pinkeye did not show any seasonal outbreak (Data not shown).

Age distribution also showed a homogeneous pattern. Separated in groups every 3 days of age after birth, the general average age distribution for the 10 groups was 45.2%, and the range was between 34.0% (group 13-15 d, P = 0.431) to 60.9% (group of 7-9 d, P = 0.248).

Chlamydia trachomatis was detected in 26 (7.83%) of 332 cases studied. In 22, *C. trachomatis* was the only pathogen detected, and in the other four cases accompanying bacteria without clinical significance were found.

Chlamydia trachomatis was not detected in the 0- to 3-, 25- to 27-, and 28- to 30-day-old groups of infants. It was present in the other seven groups, with a significant peak in the 7- to 9-day-olds (odds ratio [OR] = 2.60; 0.93 < OR < 7.06) (Cornfield 95% confidence limits; P = 0.0374, Mantel-Haenszel correction) (see Table 3). There was a tendency to higher incidence in spring and summer, but without any statistical significance (see Table 2).

A considerable decline of chlamydial incidence (cases per 1000 live births) occurred from 1995 (4.39) to 1996 (1.85). During the 1997 (1.01) and 1998 (0.78) period, a slighter decrease, independent from the general decline of conjunctivitis cases, was observed.

Chlamydia trachomatis detection by ELISA was confirmed by gene amplification, using primers that detect the cryptic plasmid. In seven cases, *C. trachomatis* was isolated in tissue cultures (McCoy's), and these strains were genotyped by RFLP of the major outer membrane protein (MOMP). Five strains were type E and two type G.

DISCUSSION

Ocular conjunctival infection in the first month of life is a health problem that occurs immediately after birth when the newborn is still at the hospital or, in a more significant number of cases, after leaving the hospital.

It was possible to detect a significant decline of the number of cases from 1995 to 1996 in the area served by the Posadas Hospital. After 1996 a steady rate of attended cases at the hospital was observed: 15.4 (1997) and 15.2 (1998) cases per 1000 live births. This rate of neonatal conjunctivitis appears to be similar to that found by Iroha et al, who reported 18 cases per 1000 live births in Lagos University Hospital.[14]

Chlamydia trachomatis infection in neonates is most often recognized by conjunctivitis that develops between day 5 and day 12 after birth.[15] In this study, a peak was noted in the group of 4- to 7-day-old infants, but *C. trachomatis* infection was detected, without statistical significance, until the 22- to 24-day age group. This profile could be related to the characteristics of longer resolving periods of evolution of some of the *C. trachomatis* ocular infections and concomitant delay of the mothers to seek medical attention.

Chlamydia trachomatis has been found in 7.83% of the studied cases; there is a clear tendency toward higher prevalence in the spring-summer season. Similar findings have been reported in Japan.[16] A decrease in incidence in *C. trachomatis* is observed in ocular diseases in children less than 30 days old from 1995 to 1998 that coincides with a general decreasing pattern of *C. trachomatis* in the Buenos Aires metropolitan area.[6,17] In *C. trachomatis* neonatal ocular infections, type E more

Table 2. Percentage of Seasonal Distribution of Positive *Chlamydia trachomatis, Haemophilus influenzae, Streptococcus pneumoniae*, and Negative Cultures

Season	*Negative Cases**	*C. trachomatis*	*H. influenzae*	*S. pneumoniae*
Winter	47.2 (P = 0.998)	5.98 (P = 0.424)	24.0 (P = 0.016)	19.20 (P = 0.036)
Spring	47.8 (P = 0.964)	11.50 (P = 0.177)	16.2 (P = 0.902)	10.25 (P = 0.272)
Summer	39.9 (P = 0.145)	7.80 (P = 0.858)	10.5 (P = 0.161)	5.97 (P = 0.070)
Autumn	56.7 (P = 0.130)	6.30 (P = 0.770)	11.9 (P = 0.297)	16.41 (P = 0.578)
Total Mean	47.6	7.9	15.65	12.95

*P-values obtained by Yates correction.

Table 3. Age-Specific Distribution of Isolated Bacteria in Neonatal Conjunctivitis*

	Age Group (Days after Birth)									
Bacteria	0–3 (n = 8)	4–6 (n = 13)	7–9 (n = 48)	10–12 (n = 68)	13–15 (n = 79)	16–18 (n = 52)	19–21 (n = 59)	22–24 (n = 24)	25–27 (n = 16)	28–30 (n = 15)
C. trachomatis (n = 26)	0	1	7	2	7	4	3	2	0	0
H. influenzae (n = 56)	1	3	4	8	12	8	9	4	3	4
S. pneumoniae (n = 41)	0	0	1	8	8	10	5	5	1	3
S. aureus (n = 29)	2	0	4	8	4	2	4	3	0	2
Staphylococcus spp (n = 18) (α-hemolytic)	0	0	0	4	3	3	3	2	1	2
Other (n = 54)	1	2	7	12	10	6	8	3	5	0
Negative (n = 158)	4	7	25	26	34	18	26	8	6	4

*382 isolates detected among 332 clinical cases: some patients presented more than one microorganism.

frequently and type G with less incidence were observed. This is original and preliminary information about *C. trachomatis* types in Argentina. Borrego et al, in Guinea, found type A (50%) and type B (50%) *C. trachomatis* to be associated with conjunctivitis strains from newborns.[18] Type E has also been detected to have the highest incidence in cervical samples from women who presented at the Posadas Hospital (Unpublished data).

Chlamydia trachomatis genotypes of eye infections reflect the genital distribution in mothers. So far there has been no conclusive evidence to associate a particular genotype with the rate of infection transfer from mothers to neonates, with the characteristic of asymptomatic or symptomatic evolution, intensity of induced pathology, or persistence.[19]

This study indicates that *C. trachomatis* is the most frequent sexually transmitted disease (STD) bacteria; however, the incidence (7.83%) is lower than that reported by Salpietro et al, in Messina, Italy, where it produced 41% of ocular infections in newborns.[20]

Arteaga et al,[21] in Caracas, Venezuela, found conjunctivitis in infants from 1 to 6 months of age related with *C. trachomatis* infection in 69.5% of cases, and Paul et al, in India, found a rate of 12.5% of *C. trachomatis* neonatal conjunctivitis.[22] It is known that approximately one-third of the infants exposed to *C. trachomatis* during vaginal delivery develop ocular symptomatic conjunctivitis as newborns. Jain et al, at the Emory School of Medicine, Atlanta, GA, USA, reported that 13.2% of infants evidenced *C. trachomatis* ocular infection and came from a group of mothers among whom *C. trachomatis* genital infection was found in 35%.[23]

In the present study, microbial growth was detected in 174 cases (52.4%); in 47.6% it was not possible to assign a bacterial infectious etiology. Almost all reports about bacterial etiology of ocular infections in newborns indicate that a significant number of negative cultures is present even when viral detection is included.[24]

It is not possible to eliminate a viral origin, but it is unlikely that an epidemic agent, such as EV70, adeno 8, or Coxsackie A24, was involved. Pinkeye of chemical origin could account for some of the cases in the first 24 to 48 hours, because treatment with 1% silver nitrate ($AgNO_3$) in water is compulsory in every live birth, in the maternity setting of the Posadas Hospital.

Among 332 cases of neonatal conjunctivitis, other microorganisms (*H. influenzae*, *S. pneumoniae*, *S. aureus*) more prevalent in this study area, colonized the ocular region only in 50% of the infants who had pinkeye. Probably they were not the actual etiologic agents, and a basic allergic or inflammatory disease is necessary for the development of bacterial overgrowth.

In this study, *H. influenzae* was associated with conjunctivitis in 16.8% of all cases, in 12.2% alone and in 4.5% associated with *S. pneumoniae*. *Haemophilus influenzae* did not show any specific difference of incidence according to age groups.

Sandstrom et al, in a case-control study, found 8 of 36 *H. influenzae* isolates in neonates with conjunctivitis compared with 1 of 60 controls without ocular diseases.[4] *Haemophilus influenzae* appears to be frequently associated with ocular pathology in newborns in the Posadas Hospital area. The profile of drug sensitivity gives a warning, because there is an elevated percentage of strains that produce β-lactamase. In contrast to the incidence of *C. trachomatis*, *H. influenzae* and *S. pneumoniae* show a significant occurrence during winter and autumn. On the other hand, Kaivonen found *S. aureus* to be more often isolated from purulent eyes than controls.[6] In the present study, *S. aureus* was found in a significant number (8.7%) of cases, whereas *S. pneumoniae* was a potential helper pathogen associated with *H. influenzae*. It is interesting to recall that 3.9 % of *S. pneumoniae* were oxacillin-resistant strains. It appears that *C. trachomatis* is a specific agent of clinically symptomatic conjunctivitis in newborns, with a reduced attack rate compared with the percentage of mothers having a current genital infection.

The question arises whether a basic inflammatory or allergic disease is necessary in the newborn prior to a *C. trachomatis* symptomatic progressive infection. The authors conclude that in the ocular diseases of newborns, in the Posadas Hospital area, detection of *C. trachomatis* by a sensitive method (e.g., ELISA and PCR) must be maintained as a routine diagnostic procedure.

The two entities, *C. trachomatis* and *N. gonorrhoeae* infection, cannot be distinguished either clinically or from purulent conjunctivitis caused by other microorganisms.[25] It is clear that several microbial pathogens are involved in neonatal conjunctivitis. These organisms have different susceptibilities to antimicrobial agents, so culture and sensitivity testing are required as a solid guide for therapy. It is recommended that the current complete protocol for laboratory tests be maintained in primary therapy for neonatal conjunctivitis.

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