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Persistence of chlamydial infection after treatment for neonatal conjunctivitis

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SUMMARY A high incidence of pharyngeal infection was found in babies with isolation-positive chlamydial conjunctivitis. *Chlamydia trachomatis* was isolated from the pharynx of 12 (52%) of 23 babies before treatment, and was reisolated from the eyes of 4 (12%) of 34 and from the pharynx of 14 (41%) of 34 after treatment. *C trachomatis* was reisolated significantly more often from babies treated only with topical tetracycline for 4 weeks (75%) than from those treated with both topical tetracycline and oral erythromycin for 2 weeks (32%). Reisolation from the eyes was associated with only minor clinical signs. Radiological signs of an inflammatory lesion in the chest were found in 2 of 8 babies examined because of persistent cough. These signs were not associated with high or rising titres of serum chlamydial antibody.

Chlamydial infection in children was recently reviewed by Ridgway.[1] Infection in the newborn infant commonly presents as a severe purulent conjunctivitis,[2–3] although mild and subacute cases have been reported. The condition is self-limiting and may resolve spontaneously within a few months. The sight is rarely compromised although micropannus and palpebral scarring can occur particularly in the absence of treatment.[4–5]

An association of chlamydial conjunctivitis with lower respiratory tract infection was first suggested by Schachter *et al.*[6] and was later supported.[7–11] Harrison *et al.*[9] reported that in 9 of 30 babies admitted consecutively to the children's hospital in Seattle with pneumonitis, *Chlamydia trachomatis* was isolated from naso-pharyngeal swabs and aspirates and high levels of chlamydial antibody were associated.

The isolation of chlamydiae from the pharynx when chlamydial conjunctivitis is present could simply reflect their presence in secretions draining from the eye via the lacrimal duct rather than colonisation of the epithelium. However, *C. trachomatis* has a high specificity for columnar epithelium and active infection of the compound columnar epithelium of the pharynx is indicated by isolation from naso-pharyngeal aspirates of infants with pneumonia in the absence of clinical and microbiological evidence of conjunctivitis.[7 9–11] A residual pharyngeal focus may therefore be a source of lower respiratory tract infection and reinfection of the conjunctiva. Theoretically it is more likely to be found in babies in whom conjunctivitis has been treated only with topical tetracycline or with antibiotics only partially active against *C. trachomatis*—such as chloramphenicol.

The purpose of this investigation was to find out (1) the pretreatment isolation rate of *C. trachomatis* from the pharynx of babies with chlamydial conjunctivitis, and (2) the reisolation rate from the eyes and the pharynx of babies who had received topical tetracycline either alone or combined with oral erythromycin.

The symptoms and signs associated with reisolation and the possible role of *C. trachomatis* in the development of lower respiratory tract infections are discussed.

Patients and methods

Pharyngeal and conjunctival swabs were taken at each follow-up examination from 34 babies treated consecutively for chlamydial conjunctivitis. The last 23 babies also had pharyngeal swabs taken at the time of the primary isolation of *C. trachomatis* from the eyes.

All babies had been referred by paediatricians: 24 had been examined in maternity units, 6 had been referred from outpatient baby clinics of the units, and 4 had been examined in children's hospitals to

Table 1 *Age at onset of conjunctivitis and at referral from paediatric units of 34 babies*

Referring unit	*Age (days)*			
	Onset of conjunctivitis		*Isolation of C. trachomatis*	
	Range	*Mean*	*Range*	*Mean*
Maternity (n=24)	1–10	6·1	4–14	8·2
Baby clinic (n=6)	2–7	5·6	12–49	20·7
Children's hospitals (n=4)	5–7	6·8	15–42	23·8

which they had been admitted after failure of treatment of conjunctivitis prescribed by the family doctor before investigation for *C. trachomatis*. The age at onset of conjunctivitis and at referral from these units is given in Table 1.

For initial investigation of outpatients and for follow-up examinations, babies and their mothers attended the Nonspecific Clinic in the gynaecological outpatient department at the Liverpool Royal Infirmary and the Royal Liverpool Hospital, or the Women's Hospital, Liverpool.

Our routine investigation of babies with conjunctivitis has been described.[3] Pharyngeal specimens were obtained with the same type of cotton-wool tipped swab as that used for taking eye specimens. Care was taken to ensure that the specimen was obtained from the mucosal surface by gently stroking the posterior pharyngeal wall. Swabs were placed in transport medium[12] and immediately delivered to the laboratory; in a few cases swabs were taken in the evening and stored overnight at 4°C.

In the laboratory, specimens were inoculated into cycloheximide-treated coverslip monolayers of McCoy cells and incubated for 48 hours at 35°C, after which they were Giemsa-stained and examined by dark-ground microscopy for chlamydial inclusions. The total number of inclusions which developed in the whole coverslip was counted. Details of all these procedures have been described.[13–14] In most cases the specimens were inoculated into McCoy cells within 2 to 4 hours of being collected from the child, but occasionally they were stored overnight at 4°C.

Babies were examined during treatment and swabs were taken at each subsequent outpatient attendance. Each mother was asked to bring her baby for examination at ages 4, 8, 12, 18, and 24 weeks. This period of observation was longer if a reisolation was obtained. Examinations were carried out by two of us (E R and I A T).

Babies were treated with either 1% chlortetracycline eye ointment inserted into both eyes 5 or 6 times daily for 28 days, or for 14 days with concurrent erythromycin syrup 30 mg/kg daily in divided dosage. A few of the earlier babies received only 7 days' erythromycin with 14 days topical treatment. In most babies treatment was given initially by nursing staff in the maternity units, and was continued at home by the mothers on discharge from hospital 2 or 3 days later.

No baby was left untreated. If a reisolation was obtained the baby was recalled and given combined treatment. There was delay in retreatment if a mother failed to keep an appointment. Swabs were repeated on reattendance to confirm the persistence of infection.

Routine radiological examination of the chest of babies who developed cough in the follow-up period was instituted in the latter part of the study. Eight babies were examined.

Clinical and laboratory investigations were carried out routinely in all mothers and, wherever possible, the fathers were examined for evidence of urethritis. All infected parents were treated.

Results

The sites of primary isolation and reisolation of *C. trachomatis* are shown in Table 2.

Primary isolation. Pharyngeal isolations were more common in older babies, being obtained from 3 of 12 babies aged <11 days, and from 9 of 11 babies aged >10 days. The inclusion count, which is a measure of the degree of infection,[13–14] was low in the pharynx (range 1–21, mean 7·6 inclusions) compared with the eye (range 5–3077, mean 1210 inclusions). There was no apparent correlation between the eye count and the presence or count of *C. trachomatis* in the pharynx.

Follow-up. The overall failure rate was 16 (47%) of 34 babies (Table 3). Of the 11 babies whose pharyngeal swabs were negative before treatment, 5 became positive during follow-up after treatment, 4 of whom had negative eye swabs. The reisolation pharyngeal swabs gave much higher inclusion

Table 2 *Sites of primary isolation and of reisolation of C. trachomatis*

Isolation	*Site of isolation*		
	Eye	*Pharynx*	*Eye and pharynx*
Primary (n=23)	11	0	12
Reisolation (n=34)	2	12	2

Table 3 *Sites of first reisolation of C. trachomatis after treatment in 34 babies*

Treatment	*Site of reisolation*		
	Eye	*Pharynx*	*Eye and pharynx*
Topical (n=12)	1	8	0
Topical and systemic (n=22)	1	4	2

counts than the primary pharyngeal swabs (range 1–1887, mean 166·1 inclusions) suggesting an established infection of the mucosa.

Reisolations from the eyes or pharynx, or both, were obtained from 7 (32%) of 22 babies treated with combined topical tetracycline and systemic erythromycin and from 9 (75%) of 12 treated only with topical tetracycline ($\chi^2 = 4{\cdot}21$, 1 df; $P = <0{\cdot}01$). Initially, for the purpose of this investigation, the two treatment schedules were given alternately but the high reisolation rate, particularly from the pharynx, of babies given only topical treatment led to our stopping this practice for ethical reasons.

There was persisting pharyngeal infection in two babies, in one for 6 weeks and in the other for 34 weeks, but there was no reisolation from the eyes of either. One, born by caesarean section to an unmarried mother, was diagnosed aged 18 days in a children's hospital and treated with topical tetracycline and oral erythromycin for 6 days in hospital and subsequently at home by the mother. *C. trachomatis* was reisolated from the pharynx at 1, 14, 18, and 35 weeks after treatment. There was persistent cough but clinical and radiological examinations of the chest were normal. The mother admitted she had had great difficulty in administering both oral and topical treatment.

The second baby received only topical treatment on diagnosis. *C. trachomatis* was isolated from the pharynx 6 and 12 weeks after treatment. No further isolations were obtained after combined treatment. A third baby, treated topically, had reisolations from the pharynx at 5 weeks and from the pharynx and eyes at 12 weeks. In this case there may have been reinfection of the eyes from the pharynx.

Five babies were preterm. Gestation ranged from 32 to 35 weeks and birthweights from 1·63 to 2·23 kg. Four of the 5 received combined treatment and no reisolations were obtained in follow-up periods of 8, 28, 34, and 34 weeks respectively. The fifth baby had topical treatment and *C. trachomatis* was reisolated only from the pharynx when aged 12 weeks.

The age at reisolation and period of follow-up after treatment are given in Tables 4 and 5.

Table 4 *Age at reisolation of C. trachomatis in 16 babies (25 reisolations)*

	Age (weeks)						
	<4	*4–7*	*8–11*	*12–15*	*16–19*	*20–23*	*32–35*
Number	2	5	4	6	2	4	2

Table 5 *Period of follow-up after treatment*

Treatment	*Time (weeks)*					
	<4	*4–7*	*8–11*	*12–23*	*24–35*	*32–52*
Topical	1			4	6	1
Topical and systemic	3	1	1	6	8	3

Clinical findings

The initial response to treatment was equally prompt with each treatment schedule. Although all babies had acute purulent conjunctivitis (Fig. 1 a and b),

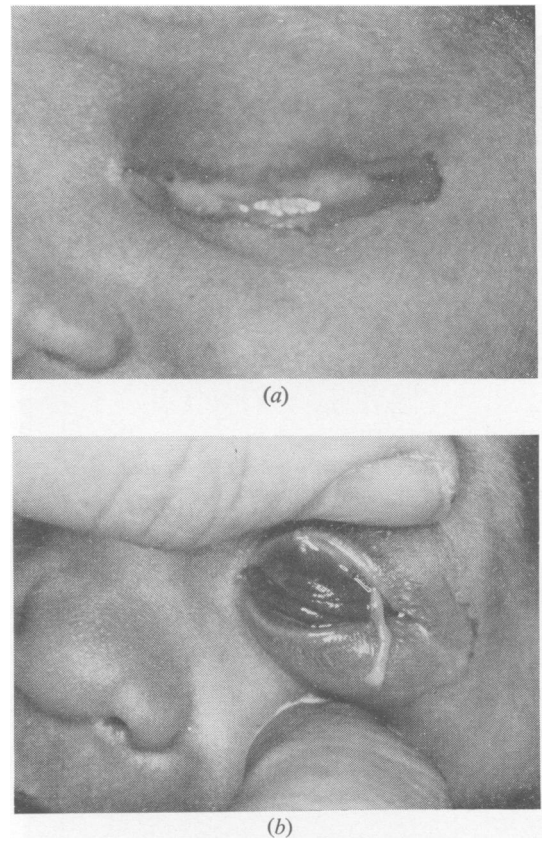

Fig. 1 (*Case 1.*) (*a*) *Palpebral oedema and purulent discharge.* (*b*) *Severe conjunctivitis with submucosal oedema. C. trachomatis isolated.*

reisolation from the eye after treatment was associated with only minor signs which were generally intermittent. The mothers complained of seeing 'puffiness', slight inflammation, and slight discharge, in some cases only when the baby was waking or crying. Two mothers were very concerned because each believed that one eye of her baby was smaller than the other. This was due to slight unilateral palpebral oedema. The clinical signs noted on eye examination were slight palpebral oedema most easily identified when unilateral, a little mucopus usually at the inner canthi, and slight to moderate conjunctivitis with or without slight mucosal oedema (Fig. 2). One baby reattended 2 weeks after treatment with bleeding from one eye for 8 hours (Fig. 3). Examination of this baby showed only slight palpebral and mucosal oedema, and moderate conjunctivitis. The blood was derived from a single bleeding point on the mucosa of the lower lid. *C. trachomatis* was reisolated from the eye and the pharynx. In our experience this finding differs from the blood-stained discharge occasionally associated with the primary isolation from an acute eye in which blood 'weeps' from the acutely congested and grossly oedematous mucosa. Clinical signs may be absent as reported in an earlier series.[15] Clinical examination of the pharynx was limited to ensuring that satisfactory swabs were taken. Observations on the presence, or absence, of pharyngitis were not made.

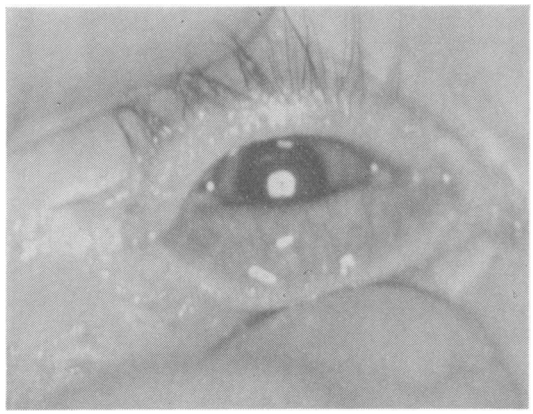

Fig. 2 *Slight conjunctivitis with a little submucosal oedema. C. trachomatis reisolated.*

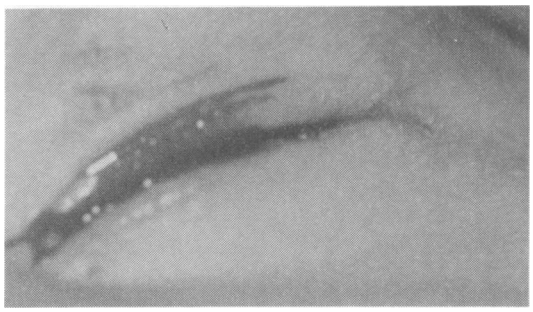

Fig. 3 *Blood presenting between the lids. C. trachomatis reisolated.*

Upper respiratory tract infections were common during the follow-up period. There was no significant difference between their occurrence in babies from whom reisolations were obtained and those from whom they were not. However, many of these babies were treated for cough with one or two courses of ampicillin by the family doctor between follow-up visits. This may have interfered with reisolation although positive swabs were obtained within a few days of the completion of such treatment in 2 cases and during the course of treatment in 1 case.

No baby was admitted to hospital with lower respiratory tract infection during the period of observation. One was admitted with gastroenteritis. None of the babies with cough failed to thrive or had symptoms or clinical signs of serious infection.

Radiological investigations. Findings were normal in 6 of the 8 babies examined. Inflammatory shadowing of the posterior segment of the right lower lobe was reported in one baby aged 16 weeks. There was a history of intermittent cough from age 6 weeks and three separate courses of ampicillin had been given by the family doctor. *C. trachomatis* was not reisolated but a course of erythromycin syrup for 2 weeks was prescribed. The chest was *x*-rayed 4 weeks later when it was reported that resolution was well under way but as yet incomplete, and again a further 4 weeks later by which time no active pulmonary disease was found. The second baby who had had a cough, particularly troublesome at night, for several weeks, was *x*-rayed at age 5 months when *C. trachomatis* was reisolated from the eyes and pharynx. A slight increase in the lung markings compatible with a resolving simple inflammatory lesion was reported. Chlamydial antibody levels were low and remained so during follow-up in both babies. IgM was not demonstrated.

Discussion

The results of this investigation indicate a high incidence of pharyngeal infection in untreated babies with isolation-positive chlamydial conjunctivitis and in those babies treated only with topical tetracycline.

Before treatment pharyngeal isolations were obtained in 52% of babies. After treatment *C. trachomatis* was reisolated from the eyes of 12%, and from the pharynx of 41% of the 34 babies followed up. Failure to include routine pharyngeal swabs would have resulted in a completely erroneous evaluation of the response to treatment, since reisolation is generally associated with absent or with only minor signs of conjunctivitis. Not surprisingly treatment with topical tetracycline and systemic erythromycin combined for 2 weeks was more effective than the 4-week course of topical tetracycline which has until recently been standard treatment and is still commonly used. *C. trachomatis* was reisolated from 7 (32%) of 22 babies receiving the former schedule and from 9 (75%) of 12 receiving the latter ($\chi^2 = 4{\cdot}21$, 1 df, $P = <0{\cdot}01$).

Reisolations from 32% of babies given combined treatment is not a good result. Possible reasons for this are inadequate treatment or failure in compliance. A lower reisolation rate might have been achieved had a 3-week course of treatment been given, although in adults with genital tract infection due to *C. trachomatis* there was no great difference in cure rate between 2 and 3 weeks of treatment. However, persistence in the pharynx rather than the eye is the problem, and failure to eradicate both aerobic and anaerobic bacteria from the throat after a standard course of the appropriate antibiotic is more common than at other sites. The choice of 2 weeks was based on the general principle that it is desirable to give babies the shortest course of antibiotics consistent with effective treatment. Compliance was certainly a problem with some mothers, even though they were carefully instructed and, in most cases, initially supervised in the maternity units. Such mothers were not irresponsible but many of them found it difficult to insert eye ointment, particularly the unsupported mothers with first babies. Some babies were said to spit out the erythromycin syrup, others to enjoy it. It is perhaps significant that no reisolations were obtained from the 4 preterm babies (birthweights 1·63–2·1 kg) who completed their combined treatment in special care baby units.

Since the radiological signs of lower respiratory tract infection in 2 babies were not associated with high or rising chlamydial antibody titres, we have no clear evidence of extension of infection from the pharynx to the chest. However, our babies received systemic antibiotics at an early age and this may have modified both the clinical and immunological response. In two recent prospective studies in the USA[10–11] maternal chlamydial infection diagnosed during pregnancy was left untreated. Evidence of chlamydial infection was reported in 70 and 61% of the babies. Only babies with conjunctivitis were treated and topical tetracycline was used. Pneumonia developed in 4 of 20 babies in one series and in 2 of 18 in the other.

The apparent rarity of chlamydial pneumonia in babies admitted to hospital in this country compared with the USA may be due to failure to consider *C. trachomatis* as an aetiological agent in Britain. However, this is unlikely in Liverpool, where the referral by paediatricians of babies for investigation of neonatal conjunctivitis has resulted in the isolation of *C. trachomatis* in 90 cases. More probably it results from a different pattern of primary medical care in the UK. Only babies whose condition causes anxiety are likely to be referred to hospital by the general practitioner and chlamydial pneumonia has been characterised as being nontoxic. Nevertheless, persistent cough creates anxiety in the mother and chlamydial respiratory tract infection may be a serious additional factor in babies whose health is compromised by other pathogens or by poor nutrition. The importance of identifying the chlamydial infection lies in the need for treatment of the respiratory infection with erythromycin rather than other more commonly used antibiotics and the need for systemic treatment of conjunctivitis.

Prevention is best achieved by treating infected mothers with erythromycin before parturition. Such treatment is necessary not only to prevent infection of the baby but to reduce the risk of postpartum pelvic infection which is a common complication in untreated mothers.[5 16–17] In addition examination and treatment of the mother's sexual partner is essential if she is not to be reinfected.

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British Paediatric Association

Annual meetings

1981	7–11 April	York University
1982	20–24 April	Aviemore Centre, Scotland
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1984	10–14 April	York University
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