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F.N. Were, MBChB, MMed, FNIC, Lecturer, A.F. Govedi, MBChB, Senior House Officer, Department of Paediatrics and Child Health, College of Health Sciences, University of Nairobi, P.O. Box 19676, Nairobi, G. Revathi, MD, Head of Laboratory Services, and J.S. Wambani, MBChB, MMed, Head of Radiology, Kenyatta National Hospital, P.O. Box 20723 Nairobi, Kenya

Request for reprints to: Dr. F.N. Were, Department of Paediatrics and Child Health, College of Health Sciences, University of Nairobi, P.O. Box 19676, Nairobi, Kenya

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F.N. WERE, A.F. GOVEDI, G. REVATHI and J.S. WAMBANI

ABSTRACT

Background: **Neonatal pneumonia is a common cause of morbidity and mortality all over the world. The problem is known to be higher in resource poor third world countries. Organisms (such as *chlamydia*) not covered by routine laboratory tests and regular antibiotic regimes may frequently contribute towards the causation of late neonatal pneumonia. It is therefore useful to gather epidemiological evidence to guide in the routine diagnosis and treatment of such infections.**

Objective: **To determine the prevalence of *chlamydia* associated pneumonia among infants developing the disease between the 7th and 30th days of life (late neonatal pneumonia).**

Design: **Cross sectional survey.**

Setting: **Newborn Unit, Kenyatta National Hospital.**

Subjects: **Fifty two newborns clinically diagnosed as having late neonatal pneumonia. They were all subjected to chest X-rays to confirm the clinical diagnosis. Nasopharyngeal aspirates for *chlamydia* antigen detection tests were then performed on all patients. The study was undertaken during the months of September through to November 2000.**

Main outcome measures: **The proportion of newborns with late neonatal pneumonia that have *chlamydia* trachomantis as the sole or contributory causative agent.**

Results: **Fifty two newborns of postnatal age between seven and 30 days were recruited. Their sex distribution was about 1:1. Thirty three (63.5%) of these infants were found with *chlamydia* in their upper airways. Thirty out of 47 available chest X-rays, representing 63.8% had evidence of interstitial pneumonitis. *Chlamydia* associated pneumonia indicated by the presence of both interstitial pneumonia and colonization of the upper air ways was present in 24 out of 47 patients, 51% of the total cases of late neonatal pneumonia. When X-rays alone were compared with our gold standard for the diagnosis of *chlamydia* pneumonia (radiology and colonization), we computed a sensitivity of 100%, specificity 73%, negative predictive value 100% and positive predictive value of 80%. Mode of delivery, birth weight and gestation had no association with nasopharyngeal colonization by *chlamydia* or actual diagnosis of *chlamydia* pneumonia.**

Conclusion: **The prevalence of *chlamydia* associated infection among newborns with late neonatal pneumonia at Kenyatta National Hospital is 51%, eight times more than that reported elsewhere. Chest X-rays appear to be a reliable diagnostic tool in this group. The use of antichlamydial drugs in addition to the regular antibiotics whenever a diagnosis of late neonatal pneumonia is made is justifiable.**

INTRODUCTION

Interstitial pneumonia is a frequent problem in immunodeficient individuals such as newborns. A typical micro-organism like *chlamydia*, *mycoplasma*, ureaplasma and a range of viruses are the usual causative agents. Ureaplasma and mycoplasma infections are more often associated with intensive care treatment involving endotracheal intubation for prolonged life support(1,2). *Chlamydia* infections in newborns have however been seen even outside intensive care units. As *chlamydia* contributes to both morbidity and probably mortality in the neonatal period, is difficult to diagnose microbiologically and does not respond to traditional antibiotics, there is a need to quantify its presence in newborn units in order to help rationalise an algorithm for empirical prescription against it.

There have been no previous reports on the

contribution of this pathogen causation of pneumonia in newborns admitted at Kenyatta National Hospital (KNH) Newborn Unit or indeed other similar units elsewhere in the country. Empirical treatment for *chlamydia* and probably other atypical non-viral organisms is however sporadically practised at the unit. The practice is presently based on clinical impression.

Neonatal *chlamydia* pneumonia is either acquired at birth (when mother's birth canals harbour the microbe) or by droplet infection from parents and newborn unit (NBU) staff. The former mode depends on the carriage rates by the mothers. Unpublished local reports indicate that about 10% of women seen for gynaecological consultation at Kenyatta National Hospital carry *chlamydia* in their birth canals(3). This may constitute a source of infection for the newborns of such mothers.

The theoretical risk of mother to child transmission is about 70% while 20% of infants of carrier mothers will develop pneumonia related to *chlamydia*(4). As the regular infection surveillance at KNH does not include *chlamydia*, its nosocomial sources remain unknown. Given a 4% global prevalence of *chlamydia* among pregnant mothers, the incidence of *chlamydia* infection is expected to be about 28/1000 live births(4).

Several studies have reported the prevalence of *chlamydia* pneumonia in groups of young infants around the world. Vaz *et al.* in Brazil in a review spanning 10 years estimated the contribution of *chlamydia* to the development of neonatal pneumonia in both term and preterm newborns to be between 10% and 20%. In this study pneumonia and conjunctivitis attributable to *chlamydia* was seen in up to 75% of newborns whose mothers were proven careers(5). This indicates a very high transmission and pathogenicity of the infection in this age group. Other workers have reported comparable findings(4).

Zar *et al.* in a hospital setting, in South Africa evaluated 100 infants less than 8 weeks old with pneumonia to describe the microbiological aetiology of their infections. Six percent of them were proved to have *chlamydia* infection(6). The authors concluded that *chlamydia* infections of the lower respiratory tract in young infants are frequent enough to warrant consistent consideration and attention. An overall *chlamydia* pneumonia prevalence of 22% was also reported in a large group of young infants in Massachusetts, USA(7). The majority of the cases occurred during the first month of life.

Dereli *et al.* in Turkey reported the presence of *chlamydia* antigens in 30% of infants less than three months old who developed pneumonia(8). Rattele *et al.*(7) and Dereri's(8) findings confirm that *chlamydia* infection in newborns is a global problem.

The clinical diagnosis of *chlamydia* pneumonia in a newborn is usually made when the patient with a rather insidious disease fails to respond to traditional antibiotics. This deduction is more accurate where the prevalence of the infection in the unit or population is known to be high. The specific diagnosis can only be confirmed by lung aspirates or biopsy evidence of *chlamydia*. These investigations are expensive, can occasionally be dangerous and are not practical in clinical settings. In routine practice, where it is affordable, chest X-rays and evidence of respiratory tract colonization are used to confirm the diagnosis of *chlamydia* or other atypical pneumonia(9).

MATERIALS AND METHODS

Case definition and recruitment: Infants admitted to the NBU who developed clinical pneumonia as defined by a respiratory rate equal to or more than 60 breaths per minute together with other constitutional signs of infection like lethargy, fever, poor feeding in absence of non-respiratory causes of tachypnoea like dehydration were eligible for this cross sectional survey. Those with clinical evidence of cardiovascular disease and aspiration were excluded. The age of onset limit was 7-30 completed days. This limit excluded those with pneumonia as part of early sepsis since this is often indistinguishable from the other prevalent early neonatal respiratory problems like respiratory distress and meconium aspiration syndromes.

Radiological methods: The diagnosis of interstitial pneumonia was then confirmed by chest X-rays. The x-rays were performed at the bedside using one of the standard potable machines. One of the investigators, a senior radiologist, reported the films. Another independent radiologist also read the same X-rays to reduce observer bias. The two radiologists had nearly 100% agreement. Only the X-rays with agreeing reports were accepted as diagnostic of interstitial pneumonia.

Laboratory methods: Nasopharyngeal aspirates were collected from each patient for *chlamydia* isolation. The collection was done using a sterile French size 4 catheter. The catheter was carefully inserted into the nasopharynx to avoid trauma and contamination. After instilling half a millilitre of normal saline the aspiration was gently but quickly done using two-millilitre syringes. From the aspirate slide impressions were made, dried in air, fixed in methanol and stored at -70° centigrade. The *chlamydia* antigens were identified using the *chlamydia*-cell if test of cellabs - Australia. This is a rapid *in vitro* direct immunofluorescence test for detection of *chlamydia* organisms in clinical specimens.

Sample: The sample of 52 was determined using the standard prevalence formula(10). Assumptions made were a probable prevalence of *chlamydia* in newborns with pneumonia of 15%, this being the midpoint of the overall prevalence reported in the 10-year Brazilian survey(5) and 10% degree of precision.

Analysis: Colonization rates and the proportion of patients with radiological interstitial pneumonia were calculated. The predictive value of chest X-rays alone for *chlamydia* associated pneumonia were also determined as sensitivity and specificity profiles.

Ethical issues: Consent was obtained from Kenyatta National Hospital research and ethics committee. The parents or guardians were also required to provide written consent before recruitment.

RESULTS

Chlamydia infection rates in late neonatal pneumonia: To estimate the possible contribution of *chlamydia* in causation of late neonatal pneumonia in this group, the nasopharyngeal colonization, presence of interstitial pneumonitis and a combination of the two (the case definition of *chlamydia*-associated pneumonia in the study) were determined (Table 1).

Table 1

The rates of chlamydia-associated pneumonia

Method of diagnosis	Total number seen	Number positive	% (Prevalence)
Nasopharyngeal colonization	52	33	63.46
Interstitial pneumonia on X-ray	*47	30	63.83
Colonization and interstitial pneumonia	*47	24	51.06

*Five radiographs were lost before reporting.

Over 60% of the newborns with pneumonia after the age of one week were also carriers of *chlamydia* organisms in their nasopharynx. The same proportion also had radiological evidence of interstitial pneumonia. Fifty one percent of the infants actually had a combination of radiological interstitial pneumonia and nasopharyngeal carriage. The latter group were deemed to have *chlamydia*-associated pneumonia.

Radiological interstitial pneumonia as a predictor of chlamydia associated pneumonia: Chest X-ray is the quickest and most convenient means of diagnosing pneumonia. We evaluated the predictive value of this tool for the definitive diagnosis of *chlamydia*-associated pneumonia. Table 2 illustrates the 2x2 table from which the predictive statistics were computed.

Table 2

Profiles of the predictive value of radiological diagnosis of chlamydia associated pneumonia

		Chlamydia associated pneumonia (positive X-ray and nasopharyngeal colonization)		
		Positive	Negative	Total
Interstitial Pneumonia On X-rays	+VE	24	6	30
	-VE	0	17	17
	Total	24	23	

The sensitivity of X-rays as a single diagnostic tool was 100% with a specificity of 73%. The positive predictive value was 80% while the negative predictive value was 100%.

Some population correlates: The possible association between mode of delivery, birth weight and gestation with atypical pneumonia was also evaluated. The following were the findings;

Colonization rates were similar between babies born vaginally (24/39, 62%) and those born by caesarean section (9/13, 69%) ($p=0.87$ X^2 test).

Seventy five percent of infants who weighed 2500 grams or more at birth had *chlamydia* pneumonia compared to 21/48 (44%) of smaller infants. This difference was however not statistically significant ($p=0.25$, Fisher's exact test).

Fifty two percent of 46 preterm infants had *chlamydia* infection compared to the 33% of the six term infants. This difference also failed to achieve statistical difference ($p=0.33$ Fisher's exact test).

DISCUSSION

Chlamydia infection was contributory to 51 % of pneumonia among the patients in this group when the combined presence of nasopharyngeal colonization and radiological evidence of interstitial pneumonia was used in case definition. This is over eight times higher than the South African series (6). Other workers though using different reference populations have reported rates between 10% and 30%. They used either the total population of infants whose mothers were infected(7,11) or the population of all sick infants seen (not confined to pneumonia)(5,8) as their denominators.

Chlamydia pneumonia is an indolent clinical disease. It is not routinely included among the investigations for late neonatal pneumonia because it is difficult to diagnose using ordinary diagnostic tests. Its prompt recognition and treatment in any center has to depend to a large extent on knowledge of the epidemiological dynamics of the infection. As the prevalence of the micro-organism is likely to vary from time to time and place-to place, deliberate and regular surveillance is essential in helping empirical prescription trends.

The evidence from the present study shows that a diagnosis of pneumonia after the first week of life (late neonatal pneumonia) has a 50 % chance of involving *chlamydia* infection. Empirical treatment of late neonatal pneumonia in this environment should therefore cover for *chlamydia.* In an attempt to establish whether the birth canal is an important source of *chlamydia* infection among these newborns, we compared nasopharyngeal colonization rates between those born vaginally (more exposed) and those born by caesarean section (less exposed). The mode of delivery had no influence on the *chlamydia* colonization of the infants. Many previous

reports have indicated that most infants are infected by the *chlamydia* that colonizes or infects their mothers' birth canals(4,7,8,11). In that case it is expected that vaginal delivery is associated with a higher risk of colonization (infection) after birth. As this was not the case in this series, it may be speculated that these infants acquired their infections after birth, which implies the possibility nosocomial route. However, since the state of the chorionic membranes (ruptured or intact) at the time of the caesarean deliveries was not evaluated, the contribution of ascending infection during labour is not known. This may have contributed to colonization even among those born by caesarean sections. The route of entry of *chlamydia* into these newborns cannot be conclusively ascertained from our results. The specific modes of transmission of *chlamydia* to newborns at any unit must be known in order to formulate control measures. Among the literature reviewed only the Brazilian study by Zar *et al* (6) reported no association between route of delivery and early colonization of newborns by *chlamydia*.

To confirm the diagnosis of *chlamydia* pneumonia, there should be microbiological evidence of the organism in the lower respiratory tree. This is both expensive and time consuming. Actual lower respiratory tract fluids (bronchiole and lung) are actually hazardous to collect in routine clinical settings. It is therefore important to devise more easily applicable investigative methods. Chest X-rays are often used for this. Used together with known epidemiology, chest X-rays should be reliable in identifying patients with *chlamydia* pneumonia. Chest X-rays as a sole diagnostic tool had 100% sensitivity and 73% specificity for the diagnosis of *chlamydia* pneumonia in this survey. This makes it an excellent screening test. A specificity of 73% is also satisfactory for diagnosing an otherwise difficult microbe to isolate. With this specificity, only 27% of the patients will receive unnecessary treatment if the test is used alone in the diagnosis of *chlamydia* associated pneumonia. The drug of choice for the treatment of *chlamydia* pneumonia is erythromycin, a relatively cheap, safe and widely available antibiotic. If erythromycin is empirically used for all cases of late neonatal pneumonia at this unit the cost of treating the extra 27% infants without *chlamydia* is still likely to be less than that of microbiological evaluation for *chlamydia*. Routine treatment of *chlamydia*-associated pneumonia is not in vain.

The disease is known to cause overall increases in hospital stay (and cost) and contributes to mortality in the newborn period(9).

Birth weight and gestation had no influence on *chlamydia* pneumonia in this group. This may however have been due to the small number of bigger and more mature infants in the study. The previous studies referenced above showed that smaller and less mature infants were more prone to *chlamydia* infection.

Our findings confirm a high prevalence of *chlamydia* upper respiratory tract colonization among infants with late neonatal pneumonia. *Chlamydia*-associated pneumonia by our definition affects half of all newborns with late onset pneumonia. We suggest that this may be the case elsewhere in the country and recommend routine inclusion of a macrolide antibiotic in the treatment of late neonatal pneumonia here and elsewhere in the country.

REFERENCES

1. Cassel, G.H., Waites, K.B., Grouse, D.T. *et al.* Association of ureaplasma urealyticum infection of the lower respiratory tract with chronic lung disease and death in very low birth weight infants. *Lancet.* 1988; **ii:** 240-245.
2. Alfa, M.J., Embree, J.E., Degagne, P. *et al.* Transmission of ureaplasma urealyticum from mothers to full term and preterm infants. *Pediatr. Infect. Dis. J.* 1996; **14:** 341-345.
3. Bukusi, E.A. HIV-1 infection and acute pelvic inflammatory disease. 1999. Unpublished Department of Obstetrics and gynaecology, College of Health Sciences, University of Nairobi.
4. Phillips, C.F. *Chlamydia* infection: In Nelson's textbook of pediatrics, 121 edition, W.B. Saunders company, Philadelphia, 1983: pp738-739.
5. Vaz, F.A., Ceccon, M.E. and Diniz, E.M. *Chlamydia* trachomantis infection in the newborn period: clinical and laboratory aspects. Experience of a decade: 1987-1998. *Revista da Associacao Media Brasileira.* 1999; **45:** 303-311.
6. Zar, H.J., Van Dyk, A., Yearts, J.K. and Harislo, D. *Chlamydia* trachomantis lower respiratory tract infections infants. *Annals of Trop. Paediatr.* 1999; **19:** 9-12.
7. Ratelle, S. *et al.* Neonatal *chlamydia* infections in Massachusetts; 1992-1993. *Amer. J. Prevent. Med.* 1997; **13:** 221-226.
8. Dereli, D. *et al. Chlamydial* infections in infants. *J. Trop. Pediatr.* 1996; **42:** 233-236.
9. Klaus, M.H. and Fanaroff, A.A. Neonatal infections: In care of the high risk neonate, WB Saunders Company, Philadelphia, USA. 1986: 262-285.
10. Lwanga, S.K. Sample size calculation: In biostatistics for medical students, East African Literature Bureau, Nairobi. 1975, pp. 122-124.
11. Jain, S. *et al.* Perinatally acquired *chlamydia* trachomantis, associated morbidity in young infants. *J. Maternal Fetal Medicine.* 1999; **8:** 130-133.