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Could urine be useful for the diagnosis of *Chlamydia trachomatis* pneumonia in infancy?

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ABSTRACT

A 9-week-old infant presented with respiratory distress. The presumptive diagnosis of *Chlamydia trachomatis* pneumonia was ultimately made in a novel manner by a positive nucleic acid amplification test on a urine sample.

We describe a case where a positive urine for *Chlamydia trachomatis* led to presumptive diagnosis of C. *trachomatis* pneumonia.

A 66-day-old female born at term by spontaneous vaginal delivery presented to the emergency department (ED) with a 10-day history of rhinitis and cough. The child was afebrile and in mild respiratory distress with a respiratory rate of 58 breaths/minute and oxygen saturations of 100% on room air. Bilateral basal crepitations were noted on chest examination. A nasopharyngeal specimen submitted in Universal Transport Media (Copan Diagnostics, Inc., Murietta, CA, USA) tested negative for respiratory syncytial virus, influenza A and B, and parainfluenza virus; by direct fluorescent antibody tests (Diagnostic Hybrids, Athens, OH, USA) negative for influenza A and B by in-house real-time nucleic acid amplification test (Dawood et al., 2009; Pabbaraju et al., 2009); and by xTAG respiratory viral panel Classic assay (Luminex Molecular Diagnostics, Inc., Austin, TX, USA) for respiratory syncytial virus, parainfluenza virus, adenovirus, human metapneumovirus, enterovirus, rhinovirus, and 4 human coronaviruses (229E, OC43, NL63, and HKUI). The child was diagnosed with bronchiolitis and reassessed at a clinic on days 16, 28, and 35 after illness onset for poor sleep and wheezing despite treatment with an inhaled corticosteroid and salbutomol. Chest radiograph at the day 28 visit showed diffuse accentuated perihilar markings and peribronchial thickening.

Clinicians then became aware that the mother was diagnosed with *C. trachomatis* genital infection (serovar unknown) based on a positive urine nucleic acid amplification testing (NAAT) on 3 occasions during pregnancy and again 11 days prior to the infant first presenting to the ED. The mother had 2 subsequent negative urines. The maternal treatment history was not clear, but she was treated at least once during pregnancy. Infant urine was submitted for *C. trachomatis* NAAT (Aptima Combo 2 assay; Gen-Probe, San Diego, CA, USA) on day 40 of illness and was positive (serovar unknown). The child had received no prior antibiotics; azithromycin was then administered for 5 days, resulting in prompt marked improvement in her respiratory symptoms. Repeat urine on day 75 after illness onset was negative using the same assay in the same laboratory. The nasopharyngeal specimen submitted at the initial ED visit (day 10 of illness) for respiratory viruses was negative when retrospectively tested by an in-house NAAT assay for *C. trachomatis* at the National Microbiology Laboratory, Winnipeg, Canada (Madico et al., 2000) (this assay was selected because the Aptima Combo 2 assay is not licensed for testing of a nasopharyngeal sample). However, a second nasopharyngeal specimen submitted for detection of pertussis in Regan–Lowe transport media 5 days prior to the positive urine (day 35 of illness) was positive for *C. trachomatis* serovar D using the same in-house NAAT assay (Madico et al., 2000; Yang et al., 1993) at the same laboratory. Two months after the azithromycin, the child had residual wheezing attributed to reactive airways disease.

The presumptive diagnosis of *C. trachomatis* pneumonia was made when the child had a compatible clinical course and a positive urine NAAT, indicating that she had subclinical genital infection. Given that most infected children are asymptomatic (Schacter et al., 1986), even detection from 2 sites in the current report (the nasopharynx and urine) does not prove that the pulmonary disease was due to *C. trachomatis*. However, the fact that both urine (collected day 40 of illness) and the nasopharyngeal specimen (collected day 35 of illness) tested positive for *C. trachomatis* and that the child clinically responded to azithromycin makes it likely that *C. trachomatis* was contributing to the respiratory symptoms, at least during the latter

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part of the illness. Blood work was not obtained so it is uncertain if the child had eosinophilia or a serologic response to *C. trachomatis*.

Perinatal transmission occurs in approximately 35% of untreated maternal genital *Chlamydia trachomatis* infections (Schacter et al., 1986). Positive cultures occur from the conjunctivae (after day 3 of life) (Schacter et al., 1986), nasopharynx (usually after 1 month of age) (Hammerschlag et al., 1982; Schacter et al., 1986), or the vagina or rectum (sometimes in the first 2 weeks but more commonly after 2 months of age) (Schacter et al., 1986). Most infected infants remain asymptomatic, but clinical conjunctivitis and pneumonia each occur in about 15% of exposed infants (Schacter et al., 1986). Conjunctival inoculation presumably occurs during vaginal delivery as *C. trachomatis* conjunctivitis usually presents in the first 3 weeks of life (Hammerschlag et al., 1982; Schacter et al., 1986). It is not clear why infants are usually older before cultures become positive from other sites.

A prospective study of 21 cases of perinatally acquired chlamydial pneumonia showed onset between day 39 and 111 after birth (Schacter et al., 1986). In a retrospective series of 30 cases of pneumonia, the age of onset ranged from day 10 to beyond day 150 of life (Chiang et al., 2005). Pneumonia usually presents as mild tachypnea and a "staccato" cough in the absence of fever, although respiratory failure and apnea have been described. About half of infants with pneumonia have eosinophilia (Chiang et al., 2005). Chest radiograph typically shows hyperinflation and bilateral infiltrates.

The standard method of diagnosing *C. trachomatis* pneumonia is to culture nasopharyngeal secretions (Chandran and Boykan, 2009). The sensitivity of genital cultures for *C. trachomatis* is thought to be below 80% (Cheng et al., 2001); sensitivity may be even lower for nasopharyngeal specimens as it is difficult to verify if an adequate sample was obtained. For genital *C. trachomatis*, it is now recognized that NAAT on a genital or urine sample has improved sensitivity over genital cultures while maintaining almost 100% specificity (Black et al., 2009). A recent study showed increased yield with NAAT versus culture in neonates with conjunctivitis (Rafiei et al., 2012). Therefore, NAAT on nasopharyngeal specimens would probably be superior to culture for detection of *C. trachomatis* pneumonia. There are reports of diagnosis of chlamydial pneumonia based on a positive NAAT on a nasopharyngeal sample (Chiang et al., 2005), but current commercial NAAT assays are not approved by the United States Food and Drug Administration for use in nasopharyngeal or conjunctiva samples (Hammerschlag, 2011). Data on the sensitivity or specificity of NAAT on nasopharyngeal samples are limited to a case series where infants had conjunctivitis rather than pneumonia. Five of 75 infants with *C. trachomatis* conjunctivitis had a positive NAAT on a nasopharyngeal sample with only 3 of the 5 being culture positive (Hammerschlag et al., 1997).

A further hurdle to diagnosis of *C. trachomatis* pneumonia is that many clinics do not have the equipment and transport media to collect nasopharyngeal specimens. It is possible that urine NAAT could detect some cases as one would presume that many infants with pneumonia would also have urethral infection. Subclinical genital infection was detected by culture in 14% of vaginal or rectal swabs from infants born to infected, untreated mothers in a previous study (Schacter et al., 1986). It seems likely that this rate would be higher with NAAT. A positive urine NAAT does not prove that pulmonary symptoms are due to *C. trachomatis* but is suggestive with a compatible clinical picture.

Further study is required as there are no previous reports of using urine NAAT to diagnosis *C. trachomatis* pneumonia. Should urine prove to be a reasonably sensitive and specific test, it would markedly simplify diagnosis and epidemiologic studies.

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