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Diagnosis of *Chlamydia trachomatis* Infection

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1. Introduction

With the use of molecular medicine as part of routine laboratory evaluation of patients, the diagnosis of infection with has undergone a metamorphosis in the last 30 years. However, it remains a debated process as molecular testing is to date not accepted as definitive in most clinical settings, and more historic testing methods like cell culture, has not been completely rendered redundant[1]. Infection with *Chlamydia trachomatis* is therefore a complex condition to diagnose, and requires a clear understanding of testing methods and the inherent advantages and disadvantages to each. The modern approach to the diagnosis of *Chlamydia trachomatis* typically involves a combination of assays as part of screening and confirmation[2].

Patients very often manifest very few clinical symptoms and rarely seek medical assistance. For this reason, continued transmission occurs to sexual partners[3] causing *Chlamydia trachomatis* to be the most common sexually transmitted bacterial infection worldwide[3, 4]. Due to these disease and pathogen characteristics, prevalence of this pathogen seems to be increasing in both developing and developed countries[5-8]. Correct diagnosis of infection with *Chlamydia trachomatis* is essential as false negative results may have significant impact on societal health[9]. Chlamydial infections has been associated with a higher risk of acquiring HIV-1 infection[4, 10] as well as cervical cancer[11] and adverse outcomes with pregnancy[12, 13]. For these reasons, early correct diagnosis of infection with *Chlamydia trachomatis* is essential to prevent long-term sequelae associated with prolonged infection.

2. Specimens, collection and transport

2.1 Clinical specimens

Chlamydia trachomatis is very often asymptomatic in female patients, but may present with cervicitis, endometritis, pelvic inflammatory disease or Bartholin abscesses[14, 15]. Urethritis and proctitis is often a secondary manifestation, found in conjunction with other sites of infection[16]. In heterosexual men, urethral infection accounts for most symptomatic cases[17, 18], with ascending infection causing epididymitis[19]. Among homo- and bisexual men, sites of infection are also predominantly the urethra[20], but further includes the

rectum[21]. Infection in infants may cause conjunctivitis as well as pneumonia, particularly in early infancy [22, 23]. Serovars L1-3 is associated with lymphogranulomavenereum (LGV), and is particularly prevalent in areas of Africa, Asia and South America[24]. Clinically, these patients present with a painless genital ulcer, which later progress to lymphadenopathy[24]. They occasionally develop systemic symptoms[25].

2.2 Specimen collection

Chlamydiae are intracellular organisms, and it is therefore essential to obtain host cells with the clinical sample to so ensure yield of organisms[2]. The sensitivity and specificity of any test for *Chlamydia trachomatis*, is highly dependent on sampling and adequacy of the sample obtained[26-28]. This holds true irrespective of testing type, whether it be culture, where viable organisms need to be obtained, or nucleic acid based testing, where non-viable genetic material can be obtained[29]. Although relatively standardized methods for sampling is advocated for direct testing, certain commercially available tests have unique sampling requirements, stipulated in the package insert[2].

In women, the endocervix is most commonly targeted for obtaining samples for culture, by utilizing either a swab or a cytologic brush. In the case of swabs, careful consideration should be taken as certain types of swabs may actually inhibit growth by being directly toxic to either the organisms or the cell culture[30]. Similarly, wooden-shafted swabs also inhibit growth. Optimal sample can be obtained using Dacron, cotton, rayon or calcium alginate-tipped swabs with plastic shafts[31]. Prior to obtaining the sample, the cervical os should be cleared of secretions and discharges, to so reduce bacterial contamination and possible toxicity. This also improves the quality and ease of interpretation of direct fluorescent antibody stains[32, 33]. Sampling should be performed by inserting the swab approximately 1-2 cm into the cervical os, rotating it, and keeping it in situ for 15 to 30 seconds. Using swabs are less likely to induce bleeding[34], which in itself may also inhibit culture, but typically has a lower cell yield than cytological brushes[28]. For this reason, some authors have advocated against the use of a cytological brush, provided sampling with a swab is performed adequately[35]. Furthermore, culture yields have been improved by combining endocervical with urethral sampling[36]. Sampling is similar to male urethral sampling, however, the swab is inserted only 1cm past the urethral opening[2].

In male patients, the anterior urethra is the site of choice for optimal sampling, especially for culture purposes. A dry swab is inserted 3 to 4 cm past the meatal opening of the urethra, rotated and removed. It is important to note that urination should best be avoided for at least 1 hour prior to sampling, as this significantly reduces the yield of cells obtained during sampling[2].

Cases of conjunctivitis should be investigated by first removing the gross purulent discharge. Thereafter, the eye should be swabbed on the palpebral conjunctival surface, to so obtains some epithelial cells[2].

In cases of LGV, sampling can be in the form of swabs from ulcers, saline aspirates from the bubo or biopsies. To ensure adequacy of deep-seated ulcers, these biopsies may be best performed under direct vision through proctoscopy[37].

2.3 Specimen transport

Culture yield is significantly improved if samples are transported to the laboratory for processing within 48 hours, and kept at 2 to 8°C during this time. The practice of freezing samples should be restricted to settings where significant delay is expected, as freezing at -70°C is associated with up to 20% loss in viability, and freezing at -20°C even higher losses[30, 38].

Various formulations of transport media have been used[39-41] as it may improve yield. This is because it typically contains fetal bovine serum to improve viability as well as antimicrobials, to suppress growth by other organisms. The formulation used is similar to transport media used for rickettsiae, but not viral transport media, as this typically contains penicillin[39, 40, 42].

2.4 Sampling for non-culture-based testing

Although typically very similar to culture based testing, non-culture based testing requires sampling and transport as specified by the manufacturers for the particular assay[43, 44]. Urine-based testing has also been advocated for molecular testing. This has the added advantage that simultaneous testing can be performed for other pathogens like *Neisseria gonorrhea* as well as being non-invasive. However, the yield on urine samples are greater if it is a first-catch sample obtained 1 to 2 hours after prior urination, to so increase the amount of columnar epithelial cells[45, 46]. If sampling is performed in excess of 3 hours after last void, specificity and sensitivity is reduced in females, but in male patients, controversy still exists[47, 48]. Some authors have reported that preceding cleaning performed in culture samples for females, should not be performed in this setting to so improve yield[46]. Novel testing methods now include sampling the vaginal introitus or vulva with promising results. The major advantage to this is that patients can self-sample[49].

3. Laboratory methods

3.1 Direct detection

3.1.1 Culture-based testing

Historically, culture-based testing was considered the gold standard for diagnosis of *Chlamydia trachomatis*, and specificity was considered to approach 100%[50-52]. This high specificity is at the cost of sensitivity, which in a best-case scenario is estimated at 70 to 85%[52]. Appropriate sampling and transport is absolutely essential to ensure organism viability.

Culture is performed using cell monolayers in dram or shell vials. Cell types permissive to infection include McCoy cells[53-55], HeLa229 cells[56, 57] and BGIMK cells[58, 59]. Certain pretreatment steps have been advocated to improve culture yield. These include administration of DEAE-dextran[56, 60], sonication[61] and centrifugation[60]. These cell cultures are maintained using Eagle's minimal essential medium (EMEM) with additional amino acids, vitamins, glucose, foetal calf serum and L-glutamine[2]. Although blind passaging has been shown to improve recovery by 3 to 10%[62], it leads to a significantly delay in obtaining results.

Following culture, the presence of *Chlamydia trachomatis* needs to be confirmed. Firstly, various stains have been used including various Romanovsky stains and iodine staining. These

methods lack sensitivity and specificity and require an experienced microscopist[54, 63, 64]. The iodine stain is based on the premise of glycogen binding. However, normal cervical cells also contain glycogen, and therefore may impact on specificity[2]. Fluorescent dye based confirmation shows improved sensitivity and specificity, as it utilizes fluorescently labeled antibodies targeting either the major outer membrane protein (MOMP) or the chlamydial lipopolysaccharide (LPS) following approximately 48 to 72 hours of incubation. Sensitivity seems to be higher with MOMP based assays, as these are more widely distributed on the cells within culture[1]. Alternatively, these methods can also be applied to shell vial based cultures, to so improve turn-around times of results and sensitivity[54, 55].

3.1.2 Antigen detection methods

Wide arrays of validated immunoassays are currently available[65-77]. Direct fluorescent antibody (DFA) testing can be utilized directly on clinical samples. As for culture-based confirmation, two antigenic sites can be utilized as targets, namely the MOMP and LPS. Assays targeting the LPS are specific to *Chlamydia* spp and are not considered specific to *Chlamydia trachomatis*. These antigens are not as widely distributed as MOMP, and sensitivity of these assays are therefore inferior to those targeting MOMP[2]. The MOMP based assays show specificity for *Chlamydia trachomatis*. These assays are validated for use on endocervical smears and male urethral swabs[78-80] but can be applied to urethral samples[78, 81], conjunctival swabs[82, 83], rectal smears[84] and respiratory samples from infants[85, 86]. DFA testing is a rapid method, with the added advantage providing simultaneous information on the quality of the sample, by way of visualizing presence of columnar epithelium in adequate samples. However, the process is laborious and requires an experienced microscopist[2]. Evaluation of DFA methods with external quality programs by the College of American Pathologist (ACP) showed significant variability in results depending on the experience level of the laboratory[80]. It has been clearly established that in the absence of a quality assurance program, more than 10% of samples will be of inadequate quality for processing[27, 35]. For this reason, specimen adequacy can be evaluated by direct examination of the sample – an advantage that only the DFA assays hold.

Immunochemical detection (EIA) can be performed either directly, targeting LPS or indirectly, by detecting anti-Chlamydial antibodies (discussed later). The LPS antigen is more abundant albeit irregularly distributed as compared to MOMP antigen. Prior to performing the EIA assays, samples are lysed, releasing large amounts of LPS thereby improving sensitivity. However, cross-reaction may occur with gram negative organisms to the detriment of specificity[62, 87-89]. To alleviate this issue, some manufacturers produce blocking assays to verify all positive results[90]. With these assays, positive tests are repeated following a pretreatment step where Chlamydial-specific monoclonal antibodies are added to the sample. True positive results will test negative on blocking assays, where false positive results will remain positive[91].

Point-of-Care testing assays are also available. These assays utilize EIA technology targeting LPS, with similar diagnostic problems with poor specificity as with laboratory based testing[65, 92, 93].

Molecular detection of nucleic acids are becoming more common, utilizing various molecular technologies. These can either utilize biological amplification (detection of ribosomal RNA) or laboratory based amplification technology like polymerase chain reaction (PCR)[94]. DNA

probes have been designed in commercially available assays targeting the 16S rRNA[95, 96]. These assays are estimated to be 1 log more sensitive as compared to EIA based assays. Specificity is reduced if samples are blood stained, as this may cause autofluorescence[2]. Some manufacturers also produce a confirmatory competitive assay, similar to those described for EIA[44, 97] to improve specificity. Furthermore, certain manufacturers offer combined assays testing for both *Chlamydia trachomatis* and *Neisseria gonorrhea*[98]. Nucleic acid amplification techniques offers the advantage of being highly sensitive and providing a platform for less invasive sampling[52]. Sensitivity may in fact be a diagnostic problem, as DNA amplification techniques have obtained positive results from environmental samples obtained from health care settings[2]. However, provided that sampling is performed with the same care as for culture, this should only be a theoretical diagnostic issue. Commercially available techniques utilized have largely focused on PCR[94, 99, 100], ligase chain reaction[101, 102] and strand displacement assays (SDA)[103], amongst others[104, 105]. Further development into real-time[106, 107] and multiplexed based platforms[108], as well as nesting steps[109] has also improved diagnostic utility.

Inherent to the nature of nucleic acid detection methods, genetic variation may lead to a reduction in sensitivity of assays. A genetic variant was described in Sweden in 2007, which contained a 377bp deletion in the cryptic plasmid[9]. This resulted in false negative results by both the Roche COBAS AMPLICOR and Abbott LCx C trachomatis assays[110, 111], and on a community level, to unrestricted spread to these strains[110, 111]. For this reason, some authorities have called for all diagnostic assays to target at least two genetic sites within the pathogen[112].

3.2 Indirect detection

Historically, serological testing has been used in investigation of women with pelvic inflammatory disease[113], ectopic pregnancies[114], recurrent miscarriages[12] and tubal infertility[115]. Despite this, serological testing to identify *Chlamydia* specific antibodies is not considered to be useful in the diagnosis of genital tract infection, for a number of reasons. Firstly, these antibodies are long-lived and do not distinguish between previous and current infection. Comparing antibody titers from acute and convalescent sera typically makes this distinction. This sampling window may be required to be as long as 1 month, and this type of diagnostic delay is not acceptable in modern laboratory medicine. Secondly, positivity is not specific for *Chlamydia trachomatis*, but rather *Chlamydia* spp., rendering interpretation of positive serology even more problematic[2]. Serological testing is considered appropriate in only two clinical settings. Firstly, use of *Chlamydia* specific IgM in the diagnosis of pneumonitis in infants, and secondly, significant rise in *Chlamydia* titers (≥ 32) in the diagnosis of LGV[24]. The practical application of this test is more difficult as the initial ulcers are typically painless and patients often do not present at health care facilities in the acute phase[2].

Various testing procedures have been employed in detecting *Chlamydia* antibodies. Historically, complement fixation (CF) was utilized in many diagnostic laboratories. For this method, a single titer of ≥ 256 is strongly predictive of LGV versus a titer lower than 32 showing good performance as a rule out test[116]. A further consideration with this assay is the requirement of biosafety level (BSL) 3 conditions[117]. Additionally, high quality antigen is not always available as these reagents are usually prepared from guinea pigs, which can be co-infected with *Chlamydia psittaci* [118].

Microscopic immunofluorescence testing (MIF) was long considered the test of choice for the diagnosis of chlamydial pneumonitis in infants, as this was utilized to identify IgM specifically[119, 120]. Historically, it was used in the description of the original 15 serovars described for *Chlamydia trachomatis* [121, 122]. This assay however is laborious and time-consuming and is therefore usually not employed as a routine diagnostic test[2] as this antigen is produced from infected egg yolk in the form of elementary bodies[2].

Enzyme immunoassay methods (EIA) are commercially available, typically targeting the LPS. A positive result in isolation does not distinguish between active or previous infection and may also be due to cross-reaction with antibodies for *Chlamydia pneumonia* or *psittaci*[123, 124]. Generally, EIA based testing is considered to be less sensitive compared to immunofluorescent-based testing[125], however, recently developed assays seem to show adequate sensitivity and specificity for use in a high throughput setting[126]. In a recent study by Baud et al, various serological platforms were evaluated. The CT-IgG-pELISA by Medac (Wedel, Germany) and automated epifluorescence immunoassay by InoDiag (Signes, France) performed adequately, but still inferior to conventional immunofluorescence assays. The CT pELISA by R-Biopharm (Darmstadt, Germany) had sensitivities and specificities comparable to gold standard assays. These authors therefore considered this assay as an alternative option in a high throughput setting[126].

4. Defining the new “Gold Standard” assay

The FDA expanded its definition of a true positive result in 1992 to include a combination of culture and non-culture based testing[127]. The Centers for Disease Control and Prevention (CDC) classifies diagnosis as definitive, presumptive and suggestive (Table 1)[87].

Definitive Requires either of criteria	1. Culture isolation with confirmation 2. Any two of the following - DFA of exudate - EIA of exudate - NAT testing
Presumptive Requires both criteria	• Presence of clinical symptoms • Detection by non-culture based test
Suggestive Requires 1 st criterion with either 2 nd or 3 rd	• Clinical symptoms • Exclusion of other causes of discharge or exudate • Sexual exposure to person with <i>C trachomatis</i> or nongonococcal urethritis, mucopurulent cervicitis or PID

Table 1. Diagnostic criteria for *Chlamydia trachomatis* published by the CDC[87]

The definition of the so-called “Gold Standard” testing assay is important for two reasons. Firstly, all commercially available tests will be measured against this standard to define performance characteristics. In the past, performance was gauged simply on culture results, leading to overestimation of sensitivity[2]. And secondly, this will impact on testing algorithms depending on local epidemiology and prevalence[128]. The issue of prevalence is particularly complex in the case of Chlamydial infection as this not impacts on test

performance, but it has also been shown that females in low prevalence settings (defined as $\leq 5\%$) seem to have a lower chlamydial load, further reducing testing sensitivity[129-131]. In its most extreme form, asymptomatic patients seem to have the worst sensitivity in testing[132]. Therefore, in these settings, the CDC advocates highly sensitive testing with confirmation of all positive samples[15].

Recently, some authors have not only advocated use of NAT testing as the only gold standard[133], but rather specific assays like the BD ProbeTec ET (Becton Dickinson Diagnostic Systems, Maryland, USA), the COBAS TaqMan ST test v2.0 (Roche Diagnostics, New Jersey, USA) and the Aptima Combo 2 (Gen-Probe, San Diego, USA)[134]. Not only are these assays highly sensitive and specific, these can be easily implemented in a high throughput laboratory[133, 135-138].

5. Comparison of methods

Currently, three molecular assays dominate molecular diagnostics of *Chlamydia trachomatis*. The Gen-Probe Aptima Combo 2 (AC2) targets the 23S rRNA molecule, whereas the Roche Cobas TaqMan CT assay targets both the cryptic plasmid and the *omp1* gene. The Abbot RealTime CT m2000 PCR targets two parts of the cryptic plasmid[139]. All of these assays can successfully detect the new variant strain, first described in Sweden[140]. Despite very good performance by all these assays, the Gen-Probe assay seems to have superior sensitivity (99.3%) and equally good specificity (99.9%) as the Abbott m2000 assay. The Roche TaqMan assay shows superior specificity (100%), but with sensitivity estimated at 82.4%[139]. These platforms have differing performance characteristics and use different pre-amplification processing steps. Since the quality of results is comparable, the true choice of assay lies by en large in the platform and pre-processing preferences.

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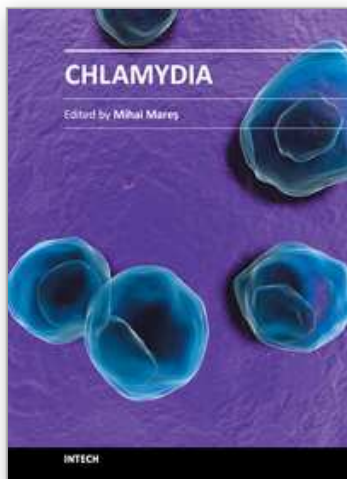
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Nowadays, Chlamydia still represents a redoubtable pathogen. Among its consequences, the blindness in children and severe impairment of reproductive health in adults are the most mutilating. Worldwide, it is estimated that six million of people suffer from post-trachoma blindness and almost 90 million become sexually infected each year. Due to its silent evolution and sexually transmission, the chlamydial infection can occur in anyone. The book “Chlamydia - A Multifaceted Pathogen” contains an updated review of all-important issues concerning the chlamydial infection. It comprises 18 chapters grouped in four major parts dealing with etiology and pathogenicity, clinical aspects, diagnosis and prevention. The new molecular data about the pathogenicity and the exhaustive presentation of clinical findings bring novelty to the book and improve our knowledge about Chlamydia induced diseases.

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