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Short Communication

Role of Chlamydiae Trachomatis in Human Reproduction - A Short Communication

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Chlamydia trachomatis, characterized by a unique biphasic life cycle, is an obligate intracellular bacterial pathogen which is responsible for the highest number of sexually transmitted bacterial infections globally. Yet its pathogenic mechanism have not been fully evaluated in view of its unique developmental cycle and obligate intracellular nature. High temperature requirement (HtrA), a critical protease and chaperone, has been previously shown to be essential for several functions and the replicative phase of Ct developmental cycles. Zhou., *et al*. designed and synthesized a novel peptidomimetic inhibitor targeting Ct HtrA using homology modeling and chemical synthesis. The inhibitor was tested in Chlamydia in the mid replicative phase and resulted in a significant loss of viable infectious progeny and diminishing inclusion size and number at a relatively low concentration. This finding not only indicates that Ct HtrA plays a critical role during the replicative phase of the Ct developmental cycle but also reveals a useful target for the design of novel antichlamydial agent [1].

In the female genital ecosystem the complex interplay between the host immune system and the resident microflora protects against urogenital pathogens, like Chlamydia trachomatis. *C. trachomatis* is responsible for urethritis and cervicitis; however most chlamydial infections are asymptomatic, and hence not treated, potentially leading to severe reproductive sequelae. Fiarco., *et al*. investigated the interaction between the levels of selected immune mediators and the community state types of cervical microbiota in a *C. trachomatis* infected women. Cervical samples from 42 *C. trachomatis* positive women and 103 matched healthy controls were investigated through the metagenomic analysis of the hypervariable region v4 of the 165 rRNA gene and the determination of the lactoferrin, interleukin 1α (IL-1α), IL-6. alpha interferon (IFN-α), IFN-β, and IFN-γ by ELISA. Overall *C. trachomatis* infection was significantly associated with a microbiota dominated by anaerobic bacteria (p=0.000002). Additionally, a network of Gardnerella vaginalis, Prevotella amnii, Prevotella buccalis. Prevotella limonensis, Aerococcus christensenii and Variovorax guang xiensis has been identified as a potential biomarker of *C. trachomatis* infection through multiple statistical approaches. Again chlamydial infection was significantly correlated with an increased production of lactoferrin, IL-1α, IL-6, IFN-αand IFN-β (p<0. 05), whereas very low levels of IFN-γ were seen in, C. trachomatis-infected women, levels similar to those detected in healthy women. Their findings showed a distinctive signatures of C. trachomatis genital infection, characterized by a specific bacterial network, constituted by anaerobes, as well as by increased level of lactoferrin and proinflammatory cytokines (IL-1α, IL-6, IFN-αand IFN- β) accompanied by a low level of IFN-γ. According to the authors this was the 1st study which investigated the association of *C. trachomatis* with the cervical levels of lactoferrin inflammatory mediators and their correlation with the different community state types characterizing the female genital ecosystem. *C. trachomatis* known as the leading cause of bacterial sexually transmitted diseases, continues to be an important public health problem worldwide for its increasing incidence and the risk of developing severe reproductive sequelae, like pelvic inflammatory disease and infertility. Specially *C. trachomatis* tend to persist in the female genital tract, leading to a chronic inflammatory state characterized by increased production of immune mediators responsible for tissue damage. Hence their study might help in broadening the knowledge on the complex interplay

between the female genital microbiota and the host immune system to *C. trachomatis* infection [2].

Human papilloma virus (HPV) and *C. trachomatis* (Ct) infection =>severe consequences for women's health. Naldini., *et al*. conducted a systematic review and meta-analysis on the evidence on HPV infection risk in women with Chlamydia and Chlamydia risk in HPV positive women. They did a Medline, Web of Science and scopus search for publications eligible until may 2018. Eligibility criteria included: assessment of HPV/Ct infection; cohort case control, cross –sectional study design; and reported risk estimation with its 95% CI for HPV infection in Ct positive women and or Ct infection in HPV –positive women. On the PRISMA guidelines meta-analysis was done using a random effect model. 48studies met the Eligibility criteria. Among women with Chlamydia the odds ratio (OR) of HPV infection is 2.12 (95% CI 1.80, 2.49) and the OR of high risk HPV infection is 2.32 (95% CI 2.02, 2.65). The OR of Chlamydia among HPV positive women is 2.23 (95%CI 1.70. 2.92). Thus concluding that HPV and Ct behave as reciprocal factors in women diagnosed with HPV infection or Chlamydia, the screening for mutual infection could represent a preventive intervention for severe reproductive health outcomes, such as cervical cancer and infertility [3].

Usually Chlamydia trachomatis infections of the lower genital tract infections are asymptomatic, hence left untreated which =>ascending infections which have long term consequences on female reproductive health. Human pathology can be recapitulated in mice with the mouse adapted strain *C. muridarum*. 8years into the post genomic area, significant advances to expand the Chlamydia genetic tool box have been made to facilitate the study of this important human pathogen. However the need for additional tools remains, especially for *C. muridarum*. Cortina., *et al*. described a new set of spectinomycin resistant *E. coli* – Chlamydia shuttle vectors for *C. trachomatis* and *C. muridarum*. These versatile vectors allowed for expression and localizalization studies of Chlamydia effectors ,like the Inc proteins ,which will be instrumental for mutant complementation studies.needs to be added which has been omitted. Additionally they explored the differential expression of specific Chlamydia genes during the developmental cycle to engineer an omc A gfp fluorescent transcriptional reporter. This novel tool allows for monitoring RB to EB conversion initiates in bacteria located at the edge of the inclusion and correlates with the post initiation of bacterial replication and inclusion size. Comparison between primary and secondary inclusions potentially suggests that the environment in which the inclusions potentially suggest that the environment in which the inclusions develop influences the timing of conversion. Altogether the Chlamydia genetic tools described here will benefit the field, as the authors continue to investigate the molecular mechanisms underlying Chlamydia host interaction and pathogenesis [4].

Rectal infection with Chlamydia trachomatis (CT) is frequent in women who deny receptive anal sex and is thought to arise from auto inoculation of the rectum from vaginal secretions. An alternate hypothesis is that oral sex inoculates and establishes gastrointestinal tract infection. Distinguishing these hypothesis is difficult. In men autoinoculation is unlikely and heterosexual men perform oral sex, but rarely participate in receptive anal exposure behaviors. Thus Batteiger., *et al*. enrolled high risk men with and without nongonococcal urethritis who presented in a sexually transmitted infection clinic in Indianapolis, Indiana. Urine and rectal swabs collected and tested for urogenital and rectal CT, Neisseria gonorrheae (NG), and Mycoplasma gentalium (MG). Men completed surveys concerning symptoms, sexual orientation, and detailed recent and lifetime oral and anal sexual behaviors. Rectal CT infections was detected in 2/84 (2.4%) heterosexual men who reported cunnilingus but no lifetime receptive anal exposure behaviors. All of the men who denied receptive anal exposure behaviors were negative for rectal NG and MG. In homosexual and bisexual men rectal CT prevalence was high (9.7%) and rectal NG (4.8%) and MG (4.8%) were also detected. Thus concluding that they found rectal CT infections in heterosexual men who reported cunnilingus but denied receptive anal exposure behaviors. Oral sex might be a risk factor for rectal CT infection via oral inoculation of the gastrointestinal tract [5].

International guidelines recommend the systematic screening of Neisseria gonorrheae (NG) and Chlamydia trachomatis (CT) infections in all men who have sex with men (MSM)engaged in unprotected sex. However, the optimal screening strategy remains unclear. Voirin., *et al*. developed a modeling approach for optimizing NG/CT screening strategy in MSM. A compartmental model of NG/CT screening and infection was implemented. NG/CT anal (A), pharyngeal (P), and urine (U) samples from MSM attending the STI clinic were used to estimate the screening rate, prevalence and incidence in a base care scenarios. Different screening strategies were evaluated: APU samples/12 months (S1), APU samples/3months

(S2), APU samples/6mths (S3), AP samples/6mths, (S4), AP samples/3mths, (S5). 2973 triplet APU samples from 1255 patients were analyzed. 485 NG and 379 CT diagnosis were observed. NG/CT prevalence and incidence estimates were 12.0%/11.1% and 40/100PY/29/100PY respectively in the base case scenario. As compared to the S2 reference strategy, the promotion of missed NG/CT diagnosis was 42%/41.2% with S1, 21.8%/22,5% with S3 25.6%/28.3% with S4 A and 6.3%/10.5% with S5 strategy respectively. As compared to S2 strategy, S1 reduced the cost of analysis by 74%, S3 by 50%, S4 by 66% and S5 by 33% respectively. The number needed to screen for catching up the missed NG/CT diagnosis was 49/67 with S1, 62/82 with S3, 71/87 with S4 and 143/118 with S5 strategy respectively. S5 appears to be the best strategy, missing only 6.3%/10.5% of NG/CT diagnosis for a cost reduction of 33% [6].

In pregnant women, untreated Chlamydial infections are associated with abortions, premature rupture of membranes, postpartum endometritis, low birth weight and transmission to the newborn. In Cordoba Argentina, there is little knowledge about the prevalence of CT in women in their third trimester of pregnancy hence Kiguen., *et al*. aimed to evaluate CT prevalence and genotypes present in Cordovan pregnant women with different age and socioeconomic status in a prospective study on women who were 35-37 weeks pregnant. 509 cervical swabs were collected. Each sample was subjected to DNA extraction and PCR for CT using primers NRO/NLO and CTP1/CTP2. Positive samples were sequenced to determine genotype. Demographic data of the patients were collected to detect a population at risk for this infection. They found a prevalence of 6. 9% (35/509) for CT infection, with 32/295 and3/214 from pregnant women with low or better economic resources respectively (p=0.0001). Results showed a significantly increased rate of 11.6% (30/258) in women under 25years compared with 2% (5/251) in patients over that age (p=0. 00003). Genotype E was the most prevalent. Thus concluding that pregnant women under 25 years old and low resources are one of the populations that the screening programmes of CT should focus on [7].

Beyuo., *et al*. conducted a cross-sectional study in 189 women with infertility who underwent hysterosalpingography at Korle Bu Teaching hospital, Ghana from september1 to 30november 2016. Demographic data, obstetric and gynecologic history; and hysterosalpingography findings were collected using a structured questionnaire. Endocervical swabs were tested for the presence of CT using a rapid antigen based diagnostic kit. Associations between the variables were assessed using bivariate analysis. Positive test results for CT were recorded among 15 participants using an overall prevalence of 7.9% (95%CI4.1-11.7%). In all 67 (35.4%) participants had abnormal findings on hysterosalpingography, with 40 (21.2%) displaying bilateral tubal occlusion. The remaining122 (64.6%) women had normal findings on hysterosalpingography. 8 participants with normal findings on hysterosalpingography tested positive for CT (prevalence 6. 6%, 95%ci2. 2%-11.0) while 7 participants with abnormal tubal appearance tested positive for CT (prevalence 10.4%, 95%CI3.1-17,7%;0=0.402). No association were found between participants characteristics and tubal pathology. Thus concluding that the prevalence of CT did not differ by hysterosalpingography findings [8].

Burkins., *et al*. carried out a single –centre retrospective cohort of patients screened for NG/CT infections at an urban academic medical centre emergency department (ED). Participants were identified through lectronic medical records. Patients were excluded if they absconded, were discharged against medical advice, or had a chief complaint of sexual assault. Patients were classified as having tested positive or negative for NG/CT and further classified as having received adequate treatment, overtreatment or undertreatment. The undertreatment group was further assessed for successful versus unsuccessful follow up. The primary aim was to determine factors associated with unsuccessful follow up in pts undertreated. Secondary aims included rate of overtreatment, and method of contact in pts with successful follow up. A total of 10,452 pts were included. Of the 456 undertreated patients, follow up was successful in 425 (93.2%) patients and unsuccessful in 31 (6.8%) patients. No history of STI's was associated as with a higher rate of unsuccessful follow up in patients undertreated for NG/CT infections (52.9% versus 74. 2%, difference = -21.3%, 95% CI-37.4%, -5.1%). Rate of overtreatment was 19. 1%, and rate of undertreatment was 46. 5%. Phone contact was the most frequent method of successful contact, which occurred in 98. 6% of patients. Thus concluding that NG/CT infections continue to be overtreated in the ED. Based on the study no history of previous STI's was associated with unsuccessful follow up in patients undertreatedfor NG/CT infections after discharge from the ED [9].

The accuracy of single serovar (L2) inclusion immunoperoxidase assay (IPA) to show serum IgG and Ig A antibodies specific to chlamydiae was compared with culture for Chlamydia trachomatis

to diagnose Chlamydial infection in 73 men with acute urethritis. Chlamydia trachomatis only was isolated from 18 (25%), Neisseria gonorrheae only from 17 (23%), and both organisms for 6 (8%). Thus 24 (33%) yielded chlamydiae.

Assays based on IgG antibodies to chlamydiae at a titer of 1/64 or more showed high sensitivity (96%) and a good negative predictive value (80%) but low specificity (13%) and agreement (48%) compared with culture. IgG antibodies to chlamydiae at a titre of 1/128 or more showed lower sensitivity (75%) but higher sensitivity (72%), negative predictive value (79%), and agreement of 79%. An appreciable (4fold or more) decrease in IgG and Ig A titres was observed in most (10) of the 15men from whom second blood samples were obtained one-2 years after treatment. Thus measuring IgG and Ig A antibodies specific to chalamydiae by IPA may serve as a useful complementary test for diagnosing and following up patients with urethritis [10].

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