Consensus by Chinese Expert Panel on *Chlamydia trachomatis*-Resistant and *Chlamydia trachomatis*-Persistent Infection

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Chlamydia trachomatis (Ct) genital infection is the most common sexually transmitted disease (STD) in China and the US. The morbidity of Ct genital infection in China has increased from 32.48/100,000 in 2008 to 37.18/100,000 in 2015.[1] The major areas of Ct infections are concentrated in the Zhujiang Delta, Changjiang Delta, Minjiang Area, and West China. In these areas, the highest incidence of Ct infection reaches 615.99/100,000 citizens. In the US, there are 1,441,789 reported Ct, which include 627.2 females and 278.4 males per 100,000 population. It is now the most prevalent STD, with its rate increasing to 22% in males and 6% in females.[2] Ct genital infection can cause epididymitis, prostatitis, cervicitis, annexitis, infertility, and atopic pregnancy, which have been identified as the major public health problems.

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More than 50% of patients with positive Ct pathogen detected by PCR method, DFA method, or cell culture are asymptomatic or have nonspecific symptoms, called hidden infections. Patients who do not receive treatment for Ct infection have a chronic infection called "persistent infection,"

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with the potential for reinfection and even complications.[3-7] Other patients still have symptoms after treatment, when the Ct infection gradually becomes chronic and persistent, it is called therapy resistant.[6,8] Therefore, experts have given more and more attention to the therapy-resistant and persistent Ct infections in the recent years.

The US CDC and China CDC renamed nongonococcal urethritis (NGU) as urogenital Ct infection in 2002[9] and 2006,[10] respectively. In addition, the agencies integrated related complications into one category: upper urogenital infection. Although the name is changed, the diagnosis and treatment have not been updated. Until now, the world has lacked a guideline or consensus on Ct therapy-resistant and Ct therapy-persistent infection.

We held a special meeting on Ct therapy-resistant and Ct therapy-persistent infection, including the diagnosis and treatment of chlamydial-relapsed and chlamydial-persistent infection, and progress on chlamydial drug resistance on August 8, 2014, in China. Specialists from the STD group of Chinese Society of Dermatology, STD group of Chinese Medical Association of Dermatology, and Chinese Chlamydia Research Center were invited to the meeting. After repeated revisions over the course of nearly 3 years, the consensus on Ct therapy-resistant and persistent infection was finally formed. For reference purposes, we have summarized the content of this consensus.

Epidemiology and Morbidity of Drug-resistant *Chlamydia trachomatis* Infection

Recently, case reports of Ct antibiotic-resistant are gradually increasing and serious.[11] In 1980, Mourad *et al*. reported on two erythromycin-resistant cases.[12] In 1990, Jones *et al*. reported five treatment failure cases that were resistant to tetracycline, erythromycin, and lincomycin.[13] A clinical survey in 1993 in the US showed that the rate of recurrence was more than 15% in patients with NGU infection after 3 months of treatment.[14] Another clinical survey in 1995 in China showed that 22.87% of patients who were routinely treated for chlamydial infection were still positive after treatment and 4.48% of these patients were stubbornly resistant after 1 year.[15] In 1997, a long-term survey showed a 20% recurrence rate for 1 year and 38% recurrence rate for 3 years.[16] In 1998, Lefèvre and Lépargneur cultivated anti-tetracycline Ct from a patient who had a treatment failure on tetracycline.[17] In 2000, Somani *et al*. reported three cases of multiple Ct resistance to azithromycin, doxycycline, and ofloxacin.[18] In 2003, a multicenter survey showed positive Ct detection in 10–15% females 4 months after treatment.[19] In 2009, according to the results of a 1788-patient survey, 24.05%, 20.58%, 12.198%, and 4.81% of patients were positive at 1-month, 3-month, 6-month, and 1-year posttreatment, respectively.[20] In 2012, a 640-patient survey showed a clinical cure rate of Ct infection of 88.91%, while the pathogenic cure rate was 78.91% when considering one negative Ct detection and 73.28% when considering two negative Ct detections.[21] The treatment failure patients increased 25.5% from 2013 to 2014 in the US. These data demonstrated that the antibiotic resistance was presenting significant difficulty in the clinical treatment of Ct. The antibiotic treatment protocols recommended in the existing guidelines were inadequate to address this growing problem.

Causes and Pathophysiological Mechanisms of *Chlamydia trachomatis* Therapy-resistant and *Chlamydia trachomatis* Persistent Infection

Clinically speaking, the mechanism of Ct persistent infection is a long-term infection. Chlamydiae undergo a biphasic developmental cycle characterized by an infectious cell type known as an elementary body (EB) and an intracellular replicative form called a reticulate body (RB). EB is an infectious, electron-dense structure that, following host cell infection, differentiates into a noninfectious replicative form known as RB. The pathogen cannot be entirely cleared with medication. Many factors can induce persistent infection in laboratory condition, such as tumor necrosis factor-α[22] interferon (IFN)-γ,[23] noncompatible cells,[24,25] amino acid deficiency, penicillin,[26,27] viruses, and phage infection.[28] Under these conditions, an abnormal and large aberrant body (AB) is induced instead of RB. AB is the main form of Ct, which is characterized by strong resistance and presents less metabolic activity. The sequence of AB induction is as follows: (1) an infected person is asymptomatic; (2) AB is resistant to antibiotics; (3) Ct DNA can be detectable but the pathogen cannot be isolated; (4) complications such as chronic pelvic inflammation, ectopic pregnancy, and tubal infertility may occur; (5) RB stops the fission and converts to an abnormal and large AB; (6) expression of OMP1 gene decreases and hsp60 gene increases; and (7) when these condition (s) such as antibiotic treatment, IFN, and malnutrition are removed, AB converts to EB.

The mechanisms of escaping the host immune defenses are as follows. (1) Ct stimulates host cells to release interleukin (IL)-2 and IFN-γ. IL-2 induces Treg replication to inhibit the host immune reaction.[29] IFN-γ stimulates tryptophan, which delays the Ct development cycle;[30] (2) Mutation of the genes related to Ct infection such as the toll-like receptor gene or NOD gene increases the risk of persistent infection; (3) The apoptosis of host cells is delayed after Ct infection since it stimulates the anti-apoptosis factors such as Mcl-2 and IAP-2;[31] (4) In the process that releases EB, the lysosome-induced membrane repair effect is activated.[32] The fusion of the lysosome membrane and broken cell membrane makes EB remain in the cells, thus causing persistent infection.

Ct-persistent infection enables survival in the host and causes complications. During Ct-persistent infection, the symptoms and Ct number fluctuate repeatedly.

Table 1: The diagnosis of *Chlamydia trachomatis* upper urogenital infection

Sex	Complications	History	Clinical manifestation and examination	Laboratory examination
Male	Prostatitis	Ct urethritis	Perineum pain; acid bilge feeling; rectum belly feeling; ejaculation pain; prostate dissymmetry enlargement, hard and pain	Pathogen culture (+), or nucleic acid detection (+), or DFA (+), or secretion IgA anti-Ct (+) in prostatic fluid
	Epididymitis	NGU	Epididymis dissymmetry enlargement, pain, swelling, hard; fever; testis may be involved	Pathogen culture (+), or nucleic acid detection (+), or DFA (+) in aspirated fluid of epididymis
	Reiter Syndrome	Sexual contact or intestinal tract infection	Dissymmetry arthritis, urethritis, prostatitis, conjunctivitis, wrapping balanitis, and palmoplantar seborrheic keratoses	Pathogen culture (+), or nucleic acid detection (+), or DFA (+) in urinary swab and HLAB27 (+)
Female	Endometritis	Chlamydial cervicitis	Abdomen pain; abnormal vaginal bleeding	Pathogen culture (+), or nucleic acid detection (+), or DFA (+) in cervical swab
	Annexitis	Chlamydial cervicitis or endometritis	Hypogastrium pain, tenderness, and rebound tenderness; irritation sign of bladder (+); fever, chill, headache, inappetence; enlarged fallopian tube or inflammatory tumor can be touched. It can lead to severe complications, such as fallopian tube adhesion and infertility	Pathogen culture (+), or nucleic acid detection (+), or DFA (+) in tubal biopsy
	Pelvic inflammation	Chlamydial cervicitis, endometritis, or annexitis	Abdomen pain, tenderness, and rebound tenderness; fever and lumbago	PMN in cervical swab >30/HP; Pathogen culture (+), or nucleic acid detection (+), or DFA (+) in endometrium and fallopian tube (+)
	Perihepatitis	Gonococcus or Ct infection	Liver area pain, fever, nausea, vomiting, and peritonitis sign	Perihepatitis in laparoscope; serum antibody against Ct (+)

Ct: *Chlamydia trachomatis*; NGU: Nongonococcal urethritis; PMN: Polymorphonuclear; DFA: Direct fluorescent antibody.

Diagnosis of *Chlamydia trachomatis* Therapy-resistant and *Chlamydia trachomatis* Persistent Infection

Diagnosis of Ct-therapy-resistant includes the following:[4,33]

1. Ct is present 3 months after CDC recommended-treatment, with or without symptoms. Sexual contact must be exclusive to avoid reinfection;
2. Confirmation of the continuous presence of Ct: Two of three detections per month after treatment are positive, except for testing errors and reinfection. Pathogen detection methods include: (1) positive Ct DNA detection 2 months after treatment, especially for the same serotype or multilocus sequence type (MLST) as the pathogen before treatment; (2) Ct direct fluorescent antibody (DFA) is positive 1 month after treatment; and (3) Ct cell culture is positive at 3-month follow-up.

The diagnosis can be confirmed when the first and second criteria are met. If available, drug sensitivity testing can be performed for antibiotic resistance testing or resistant gene tested in purified Ct.

Diagnosis of Ct-persistent infection includes the following:[5,7,33]

1. Ct is continuously present for 3 months with or without symptoms. Sexual contact and treatment must be exclusive;
2. With long-term infection, patients who are confirmed as Ct positive have upper urogenital infection [Table 1].

The diagnosis can be made when either the first or second criterion is established.

Methods to confirm Ct continuous existence: Two out of three pathogen detections per month are positive, except for testing errors and reinfection. Pathogen detection methods include (1) Ct DNA detection positive, especially for the same serotype or MLST type, as before; (2) Ct DFA detection positive; and (3) Ct cell culture negative for the first generation and positive for the following generation. The inhibited Ct may disinhibit *in vitro* culture in subsequent passages. We can confirm that Ct continuously exists when it meets one of these three standards. When present, abnormally enlarged inclusions (AB) detected by electron microscopy or Hsp60 antibody detected by serological testing indicate Ct-persistent infection.

We choose the 1st, 2nd, and 3rd month as the follow-up time after treatment for the following reasons. First, the medicines used in Ct treatment have a long half-life period, acquiring more time to be resolved. Second, Ct grows very slow, especially in an inappropriate environment. Third, there are no Ct pathogens available by swab collection. Therefore, the examination should be scheduled after prostatic fluid ejection or before morning urination. Finally, the sensitivity and specificity of the test method were in the consideration.

Clinical Advice for *Chlamydia trachomatis*-Persistent Infection and Therapy Resistance

1. The most important reason for treatment failure is inadequate medicine or dosage and insufficient treatment course, which all tend to induce the drug resistance and persistent infection. Therefore, appropriate education, standard, and enough-course therapy[8,33-35] should

be given to diagnosed patients (medium quality of evidence, strong recommendation)
2. We can change the medicines[4] or prolong the therapy course[4,5,34-37] for those therapy-resistant patients. For example, we can use doxycycline or clarithromycin for 14 to 21 days. We suggest the combination of antibiotics for resistant cases.[5,18,38-41] The combination of azithromycin and moxifloxacin is the first choice. We do not suggest the use of minocycline for combination therapy (weak quality of evidence, strong recommendations)
3. Patients who present persistent infection without an upper urogenital infection should be treated following the CDC recommended-treatment (medium quality of evidence, strong recommendations). Once the patients receive any treatment, they should be treated as therapy-resistant patients[7] (weak quality of evidence, strong recommendations)
4. Patients who have persistent infection with upper urogenital infection should be treated for the corresponding complications for at least 1 month[7,42] (weak quality of evidence, medium recommendations). Treatment for 3–6 months can only be used in some special cases (weak quality of evidence, medium recommendations). For patients who are coinfected with other bacteria, other antibiotics should be used accordingly[5] (medium quality of evidence, strong recommendations)
5. It needs more evidence to support the enhancement of the immune system as an adjuvant treatment for the therapy-resistant and therapy-persistent infections[38,43-45] (weak quality of evidence, weak recommendations)

Ct fights against the antibiotic treatment and the immune system in the persistent condition. It limits the effect of the treatment and clearance of Ct.

Until now, there has been no guideline for Ct therapy-resistant and Ct persistent infection. The STD guideline of the US CDC considers persistent infection as reinfection with bacteria, mycoplasma, or anaerobic bacteria. The recommended treatment is only to repeat treatment with azithromycin, moxifloxacin, and metronidazole, but in many cases, it does not work.

The experts have tried treatment with a combination of two or more antibiotics and prolonged the treatment course (3–6 months) for Ct infection. Other experts tried to enrich the medicines with D-L lactide-glycolide complex and transfer the Ct form from RB to AB. However, these novel methods are still under development.

Other experts have attempted to improve the drug sensitivity testing, find new medicines, and investigate vaccines and specific bacteriophages for clinical usage.

Our Chinese guideline for Ct urogenital infection is referred to as a foreign guideline. Evidence based on the medicines of Chinese groups is limited. We should complete these data to make a characteristic Chinese guideline for chlamydial treatment.

In conclusion, in the past, experts gave a favorable evaluation of the antibiotic treatment of Ct. They had suggested that the hidden infection is the major reason for persistent Ct infection and that once Ct infection was confirmed, it could be easily cleared by antibiotics. But the fact is that therapy-resistant and therapy-persistent infections exist, which brings us a greater challenge in the diagnosis and treatment of Ct. We should have a clear understanding of therapy-resistant and therapy-persistent infections and explore possible solutions so that Ct infection can be controlled and its complications can be reduced in the future.

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Conflicts of interest

There are no conflicts of interest.

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