COUNTY OF SAN LUIS OBISPO
PUBLIC HEALTH LABORATORY

Messenger

JUNE 2018

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Chlamydia Treatment Failure: Antibiotic Resistance or Something Else?

The Public Health Laboratory has worked with community providers for a number of years in the setting of an apparent antibiotic treatment failure of a genital *Chlamydia trachomatis* (CT) infection. Typically a provider phones the laboratory after administering a one-gram dose of azithromycin and finding that a patient with symptoms reports no relief or a patient with no symptoms fails a test-of-cure.

Note that molecular amplification tests are routinely performed by most public health and clinical laboratories. Using this method, test-of-cure for CT infection should not be performed until at least 30 days after the antibiotic is administered. It is well established that nucleic acid remnants (i.e., the DNA target for molecular amplification tests) are not cleared for at least three weeks for the majority of treated patients. Some studies have shown that nearly all cases are cleared by four weeks, but those patients that still show a positive result are not followed further to ascertain if shedding of dead CT cells continues.

This one-month test-of-cure benchmark using molecular amplification tests contrasts with the use of culture to detect CT, a method that has been largely abandoned in favor of the more sensitive and faster molecular amplification tests such as transcription mediated amplification (TMA) and polymerase chain reaction (PCR). Culture detects viable CT cells. A test-of-cure using culture at one week post-treatment is appropriate.

Recognizing that methods of detection differ, the question invariably remains if the test-of-cure detects a "fail:" was the patient re-infected, or was the patient persistently infected? Further, if the antibiotic treatment failed, was the reason the development of antibiotic resistance?

Testing of CT for antibiotic resistance requires that culture be performed. The specimen must be placed in a viral transport medium (to keep this obligate intracellular bacteria-like pathogen alive) and then exposed to a monolayer cell culture in the laboratory. Lab scientists monitor the cell culture for characteristic cytopathic effect, then harvest live CT cells. The live CT cells must then be added to multiple cell cultures with varying amounts of an array of antibiotics to determine if resistance is present. This is a heroic laboratory effort, one that previously was performed by the CDC but has since been abandoned.

New Study: Resistance or Persistence?

Recently Dr. Robert Suchland and colleagues published a landmark research study (J Infect Dis vol 215, p 1657-1665, 2017) that points to persistence of CT

in infected but treated men and women. They conducted whole genome sequencing (WGS) analysis on live CT cultures obtained from serial collections of specimens from individuals over several years. Their data from five of seven individuals showed compelling evidence for the ability of these patients to harbor the same strain of CR for three to five years.

This study could only be performed because researchers at the University of Washington have accumulated a legacy collection of CT isolates, obtained by the now rarely-performed cell culture—coupled with repetitive cultures of infected individuals over decades.

This report might be accurately referred to as a “freezer study” that needed to wait until such time that technology advanced to the point that it could incontrovertibly distinguish a persistent infection from a reinfection. That technology is whole genome sequencing.

WGS analysis can indisputably demonstrate that individuals from whom the same serotype of CT was repetitively recovered were not the result of new infections with same serotype but the same strain persisting. WGS provides the actual DNA sequence and can demonstrate the accumulation of few mutations in the same strain in contrast to a new strain that might be the same serotype but show scores or hundreds of base changes. Remarkably, one individual in the study yielded a strain recovered three years apart that did not accumulate a single base change.

Patients were treated with appropriate antibiotics—sometimes more than once—but the treatment did not eradicate the infection. In fact, three patients showed apparent clearance of CT by negative cultures only to later show a positive culture with the original infecting strain.

So another question: how did the organism evade being destroyed by antibiotics when no mechanism of resistance can be discerned?

This is a question researchers are continuing to explore, and we will share updates in this space as they are available.

If you find that a patient seems to remain persistently infected with CT after appropriate treatment with antibiotics, please contact the Public Health Laboratory director at 805-781-5512 to discuss the case.