

Region II Laboratory Update

CDC National Infertility Prevention Project

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Laboratory Update

1. Natural History and Immunobiology of *Chlamydia trachomatis*
2. Verification and Validation of Alternate Specimens (e.g. rectal, pharyngeal, etc.)
3. CDC Laboratory Guidelines for CT/GC

Natural History and Immunobiology (Background)

- CDC National Infertility Prevention Project
 - Initiated in 1988
- Chlamydia positivity fell in most of the IPP regions
- Chlamydia rates started to stabilize or rise slightly in many of the IPP regions
 - More sensitive tests?
 - Testing different populations?
 - Not testing enough males?
 - Other reasons?

Natural History and Immunobiology (Background)

- Arrested Immunity Hypothesis
 - Dr. Robert Brunham, et.al.
- “Chlamydia immunity takes time to acquire, it is of interest that experiments in murine (mouse) models of chlamydia infection clearly show that early antibiotic treatment abrogates the acquisition of immunity and heightens susceptibility to reinfection.” JSTD December 2005

Chlamydia Immunology and Control Expert Advisory Meeting

Atlanta, April 23-25, 2008

- Highlight the key questions related to chlamydia natural history, pathogenesis, and immunobiology that have the most important implications for control of chlamydia and its sequelae
- Assess extent to which existing data address these key questions, especially with respect to their potential relevance to prevention programs
- Identify important remaining gaps in knowledge that would have implications for prevention

Chlamydia trachomatis

Some of what we know

- Pathology is primarily a function of the host-response
 - Little intrinsic toxicity
- Protective immunity has been demonstrated in animal models or animals naturally infected with related chlamydiae
 - Mice, guinea pigs, sheep etc
- Susceptibility to reinfection is common
 - High rates of reinfection
 - Early Tx of mice resulted in a disruption of immunity

Some of what we don't know

- Development of pathology poorly understood
 - How long?
 - Predisposing factors?
 - Reinfection or persistent infection?
- Development of immunity that protects against subsequent CT infections has not been conclusively documented in humans
- Human data is lacking (absent) on the mechanisms associated with reinfection
 - Bacterial?
 - Host?

Chlamydia trachomatis

Some of what we know

- Screening and Tx reduce the natural duration of infection
- Despite screening, reinfection rates seem to be increasing
 - Brunham et al JID 2005
- Antibiotic resistance has not been demonstrated among human CT isolates
 - It has been shown in pig isolates

Some of what we don't know

- How long does CT persist if left untreated?
 - Brazilian data suggests most half of the infections are cleared after a year and all are cleared by 5 years
- What are the reasons for increases in reinfection rates?
 - Better Dx tests
 - Increased / more targeted screening
 - Bacterial changes
- Why are some CT infections more difficult to treat?
 - Golden et al NEJM 2005

2010 National STD Prevention Conference

March 8-11, 2010

Atlanta, Georgia

B4 Symposium -The Natural History and
Immunobiology of Genital *Chlamydia*
trachomatis Infections and Implications for
Control of Chlamydia and its Sequelae:
Findings from the CDC Chlamydia Immunology
and Control Expert Advisory Meeting

B4 Symposium

Introduction: Immunobiology of *Chlamydia trachomatis* Infection and Implications for Control of Chlamydia and its Sequelae – Stuart Berman, MD, ScM (CDC)

Duration of Untreated Uncomplicated Genital *Chlamydia trachomatis* Infection and Factors Associated with Chlamydia Resolution – William Geisler, MD, MPH (University of Alabama)

Risk of Sequelae Following *Chlamydia trachomatis* Genital Infection in Women – Fujie Xu, MD, PhD (CDC)

Pathogenesis of Genital Chlamydia Infection and Implication for Chlamydia Control Programs - Toni Darville, MD (University of Pittsburgh)

Evidence for Protective Immunity to *Chlamydia trachomatis* Genital Infection – Byron Batteiger, MD (Indiana University)

Putting it All Together: Integrating Basic Science and Epidemiologic Findings to Inform Chlamydia Control Programs – Sami Gottlieb, MD, MSPH (CDC)

Conclusion(s)

“At this point in time, we have insufficient evidence to link the slight rise in chlamydia rates to the immunology of chlamydia and therefore, no specific recommendations can be made to chlamydia screening programs” - Steece



Verification and Validation of Alternate Specimens

- Rectal and pharyngeal swabs
 - Encourage manufacturer to seek FDA clearance
 - External specimen bank has been established
- Home collected vaginal swabs
- APHL / CDC STD Steering Committee Workgroups have developed Verification Protocols
 - Involved CMS (CLIA)
 - Part of revised CDC Laboratory guidelines

Verification and Validation of Alternate Specimens

Requestor should send an email to Ms. Carol Farshy (cef1@cdc.gov) asking for assistance

Ms Farshy will send them an email requesting certain information so CDC can triage the requests

Verification and Validation of Alternate Specimens

- 1) Type of nucleic acid amplification test that will be used to test rectal and pharyngeal specimens in your laboratory:
- 2) Approximate number of clinical enquires received to test rectal and pharyngeal specimens for *C. trachomatis* and *N. gonorrhoeae* over the past 6 months:
- 3) Approximate number of clinical specimens tested from men who have sex with men (indicate if you are unable to determine this estimate):

Verification and Validation of Alternate Specimens

The number of available specimens is extremely limited and CDC will prioritize the requests according to anticipated volume/need.



Guidelines for the Laboratory Detection of *Chlamydia trachomatis* and *Neisseria gonorrhoeae* Testing

Recommendations from the expert
consultation meeting

January 13-15, 2009

Framework

Experts:

- Public Health Laboratory Directors
- STD Program Directors
- STD Clinicians
- STD Laboratory Researchers
- FDA and CMS

Committee Members

Stefanie Akselrod
FDA

James Beebe
PHL, San Luis Obispo, CA

Gary Budnick
PHL, Connecticut

Joan Chow
CA Dept of Public Health

George Dizikes
PHL, Illinois

Yetty Fakile
CDC

Dennis Ferrero
CA Assoc. of PHL Directors

Charlotte Gaydos
Johns Hopkins University

Tom Gift
CDC

Sarah Guerry
LA County DOH Medical Director

Bob Johnson
CDC

Julius Schachter
University of California

Steven Shapiro
CDC

Shari Shea
APHL

Melissa Singer
CMS

Rick Steece
National IPP Program

Lisa Steele
CDC

Bobbie Van der Pol
Indiana University School of Medicine

Katherine Whitaker
FDA

Dean Willis
PHL, Florida

Kelly Wrobleswski
APHL

Scott Zimmerman
PHL, Erie County, NY

Framework

Target Audience:

- Laboratory Directors, technicians, clinicians and disease control personnel

Key Questions:

- Refinements or gaps from the 2002 “Screening Tests to Detect *Chlamydia trachomatis* and *Neisseria gonorrhoeae* Infections”
- Reviewed literature and prepared tables of evidence prior to consultation meeting at CDC

Overview of Key Questions

Performance Characteristics:

- Sensitivity and specificity of reported tests stratified by anatomic site

Screening Applications:

- Optimal specimen type
- Economic considerations

Laboratory Confirmation:

- Repeat testing
- Medico-legal issues

Meeting Summary: Performance Characteristics

All culture and non-culture tests may generate false-positive results

- Clinician education

Nucleic acid amplification tests (NAATs) have superior performance to all other tests

- Performance characteristics comparisons will be based on published data
- These are the tests labs should be using to detect CT and GC regardless of presentation

Culture is still useful in certain circumstances

- GC susceptibility testing
- Detect mutant strains
- Should be maintained

Meeting Summary: Performance Characteristics

Serology

- Should not be used for the Dx of non-LGV CT infections
- Should not be used for the Dx of LGV rectal infections
- Useful for the Dx of inguinal LGV infections

Direct Detection of LGV

- All FDA cleared NAATs detect LGV and non-LGV CT but are unable to distinguish the strains
- Homebrew assays have been reported for the direct detection of LGV but the data are insufficient to make a recommendation on their utility

Meeting Summary: Performance Characteristics

Need for additional data:

- Utility of LGV specific tests
 - Clinical and laboratory
- Studies on the length of time that newer NAATs will remain positive due to the presence residual DNA after treatment
- Performance of NAATs with ocular specimens

Meeting Summary: Screening Applications

Vaginal swabs are the optimal specimen type for use with NAATs

- Studies demonstrate equal performance to endocervical swabs and slightly better performance than urine
- Ease of collection and transport

Meeting Summary: Screening Applications*

Vaginal swabs are the optimal specimen type for use with NAATs

- Studies demonstrate equal performance to endocervical swabs and slightly better performance than urine
- Ease of collection and transport
- Vaginal swab and urine specimens are not intended to replace cervical exams and endocervical specimens for the Dx of female urogenital infections
- Urine is the preferred specimen type for testing males with NAATs

Meeting Summary: Screening Applications

- NAATs have superior performance to culture for the detection of **rectal** CT and GC infections
- NAATs are not cleared for rectal specimens by the FDA
 - CDC funded an external specimen bank to facilitate an off-label establishment study
 - Protocol and guidelines developed by the APHL/CDC STD Steering Committee
 - www.aphl.org/aphlprograms/infectious/std/Documents/NAATRectalSwabs.pdf
 - These are not prescriptive and must be reviewed by local CLIA surveyors

Meeting Summary: Screening Applications

NAATs have superior performance to culture for the detection of **pharyngeal** GC infections

- Too few pharyngeal CT infections for a meaningful comparison
- Some NAATs report cross-reaction and these may require repeat testing by an alternative method
- NAATs are not cleared for pharyngeal specimens by the FDA
- CDC funded an external specimen bank to facilitate an off-label establishment study
- Protocol and guidelines developed by the APHL/CDC STD Steering Committee
 - www.aphl.org/aphlprograms/infectious/std/Documents/NAATThroatSwabs.pdf
 - These are not prescriptive and must be reviewed by local CLIA surveyors

Meeting Summary: Screening Applications

Pooling specimens for testing with NAATs is an acceptable method to reduce costs without compromising performance

Meeting Summary: Laboratory Confirmation

Routine repeat testing of NAAT positive specimens is not recommended for CT

Routine repeat testing of NAAT positive specimens is not recommended for GC unless there are a significant number of false-positive test results, in clinical studies, due to cross-reaction with non-gonococcal *Neisseria* species

Meeting Summary: Laboratory Confirmation

Medico-legal issues (ASM Symposia 05-2010)

- Data supports the use of NAATs in adult cases of sexual abuse
- Limited data on the use of NAATs in cases involving children

Guidelines for the Laboratory Detection of *Chlamydia trachomatis* and *Neisseria gonorrhoeae* Testing

Next Steps

- Meeting summary available on APHL website
 - www.aphl.org/aphlprograms/infectious/std/Documents/CTGCLabGuidelinesMeetingReport.pdf
- Publish background papers in a journal supplement
- Publish the entire revised laboratory guidelines document as a Reports and Recommendations supplement in MMWR



The End - Questions



Lots of tears

Sensitivity of Different Specimens by Three Different Assays

Assay	FCU	Cx	S-vag	C-vag
TMA	72%	89%	93%	90%
PCR	84%	91%	91%	93%
LCR	98%	96%	98%	100%
Combined	81%	91%	93%	93%

FCU – first catch urine, Cx – endocervix, S-vag – self-collected vaginal swab, C-vag - Clinician collected vaginal swab. Schachter J, et al. JCM 41;2003:3784