Use of a Rapid Turnaround Test for Gonorrhea & Chlamydia to Improve Treatment of Women Presenting with Possible Sexually Transmitted Infections

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Abstract:

In the Emergency Department (ED), patients frequently seek medical treatment for vaginal complaints consistent with a possible sexually transmitted infection (STI). It is known that for our inner city population in Baltimore, Maryland, providers have a low threshold to initiate treatment for *Neisseria gonorrhoeae* and *Chlamydia trachomatis* in the ED prior to knowing the results of diagnostic tests. This is due to the delaying in receiving the results and the possible consequences of leaving an infected patient untreated. Specifically, it has been shown that untreated infections leave patients at increased risk for development of pelvic inflammatory disease, tubo-ovarian abscess, cancer, infertility, pregnancy complications (including ectopic pregnancy) and increased shedding of the human immunodeficiency virus amongst other morbidities (CDC, 2014). Currently, testing at our facility for gonorrhea and chlamydia involves sending urine or cervical specimens to an off-site laboratory for polymerase chain reaction (PCR) evaluation. Results of this testing are not available for up to 2 to 3 days after the specimen is obtained. Empiric treatment is often given in the ED because of this delay in obtaining results and the difficulties surrounding patient follow up from the ED. Some patients are not offered treatment despite having symptoms suggestive of a sexually transmitted infection. Overtreatment brings up concerns relating to antibiotic resistance, increased healthcare costs and potential for adverse reactions to the antibiotics (Newman et al., 2007). Undertreatment of patients increases their risk of developing complications related to the infection. The use of a rapid-turnaround test (RTAT) could potentially provide results in as little as 90 minutes while the patient waits in the ED. The same factors hold true for the care of patients in the recently opened Urgent Care Center at UMMC. The Urgent Care Center is staffed by faculty physicians and nurse practitioners from the Department of Emergency Medicine and many, but not all, patients with complaints consistent with STI are now managed in the Urgent Care Center. This study aims to determine if use of a RTAT improves the appropriate treatment of patients with signs and symptoms suggestive of a STI. Additionally, the effect that this testing would have on healthcare costs and its impact on patient length of stay will be analyzed.

Research Plan

A. Specific Aims

The study aims to assess whether an FDA-approved rapid turnaround test (RTAT) for *Neisseria gonorrheae* and *Chlamydia trachomatis* infections will lead to more appropriate antibiotic prescription in the emergency department.

Secondary outcomes include the RTAT's effect on length of emergency department stay, result congruence with the PCR method regardless of specimen source, result congruence with PCR method differentiating between urine and cervical specimens, estimation of the effect of utilization of the RTAT will have on healthcare costs, its impact on satisfaction, and on further healthcare utilization.

Null hypothesis: Point of care use of the GC/CT RTAT in female ED patients for whom there is a suspicion of either disease results in no more appropriate antibiotic prescription than in patients who receive empiric therapy before GC/CT PCR results return.

B. Background Significance

Infections with *Chlamydia trachomatis* and *Neisseria gonorrhoeae* are the most commonly reported sexually transmitted diseases in the United States. In 2014, there were 1,441,789 cases of chlamydia and 350,062 cases of gonorrhea reported in the US (CDC, 2014). Baltimore ranks 4th in US metropolitan areas for rates of chlamydia at 1245 cases per 100,000 and 17th for rates of gonorrhea at 314 cases per 100,000 (CDC, 2014).

Untreated infections leave patients at increased risk of pelvic inflammatory disease, infertility, ectopic pregnancy and shedding of the human immunodeficiency virus among other morbidities (Johnson and Mak, 2002). Because of this, providers have a low threshold to initiate treatment for gonorrhea and chlamydia. In a previous retrospective analysis done at this hospital and a nearby community hospital it was found that patients were inappropriately treated 21% of the time (Holley et al., 2015). Inappropriate treatment is defined for the purpose of this study as administration of antibiotics to treat GC/CT in the absence of GC/CT infection or failure to give antibiotics in the presence of GC/CT infection. For the purposes of the study the "gold standard" result will be that of the PCR test and not the RTAT. By evaluating the impact of a rapid turnaround test for GC/CT, we will determine if there is a reduction in the rate of inappropriate treatment. Furthermore, we will analyze the economic, temporal, and qualitative impacts of altering the current paradigm.

C. Research Design

A prospective, nonblinded, randomized controlled trial will be conducted at the Adult Emergency Department at the University of Maryland Medical Center and Adult Urgent Care Center, which is managed by the Department of Emergency Medicine, located in Baltimore, Maryland.

Sample size calculation was performed assuming that the control group will be given the wrong treatment 21% of the time. It is assumed that the use of the rapid TAT will reduce this by about 95%. The following variables were used to calculate the sample size: alpha = 0.05 power = 0.8 P0 = 0.21 P1 = 0 M = 1. It was determined that 43 patients are required in each group. Assuming a dropout rate of up to 10% this study will enroll 48 patients into each of the study groups.

Patients who consent to participation will be randomly selected into either the control group or the experimental group.

i. Control group - GC/CT testing done only via standard PCR test
ii. Experimental group - GC/CT testing done using both rapid TAT and standard PCR tests

Subjects will be randomly assigned to either the study or control groups. Randomization will be performed at the level of the patient, with the study team member using blind-sequenced subject folders. Patients will be assigned a sequential subject number with a corresponding folder for the study team member. This folder will contain the randomly assigned treatment allocation and data collection forms. Randomization for the subject folders will be performed using an online randomization tool.

Study team members will assess patients for inclusion and exclusion criteria. Patients who meet criteria will be invited to participate in the study.

Informed Consent Process: Patients who meet study criteria and desire to be a part of this study, will be consented prior to procedure. A copy of the consent and research proposal will be provided and reviewed with the patient. This study will be voluntary and confidential. All patient identification information will be kept in the principal investigator's locked office.

Study Location: Study will be conducted in the Adult Urgent Care Center and Emergency Department at the University of Maryland Medical Center.

All study participants that will be enrolled will undergo standard of care testing to evaluate for a sexually transmitted infection. If the result of the RTAT in the experimental group is "invalid" treatment will still be at the discretion of the provider using the information available including history, physical and determination of risk. No repeat testing with the RTAT is allowable as part of study procedures.

During the subject screening and consent process, we hope to identify subjects that are not willing to wait for the results of their testing should they be a part of the experimental group and not enroll them in the study. Should these subjects enroll in the study and subsequently change their mind about waiting for their results, they may choose to withdraw from the study and leave. If the RTAT sample is already being run on the machine at the time of the subject's departure, the subject will be contacted with the test result. If the test result is positive they will be counseled about appropriate next steps taking into account whether or not they received empiric treatment. All study participants that will be enrolled will undergo standard of care testing to evaluate for a STI. Per usual care at the University of Maryland Medical System, the clinical provider determines treatment at the time of initial evaluation using all the available clinical information. For patients assigned to the intervention group- If the subject leaves prior to completion of the RTAT then the clinical provider still determines treatment based on the information available.

In a study published by Gaydos et al in 2013, the Cepheid RTAT for chlamydia in females demonstrated sensitivities for endocervical, vaginal, and urine samples of 97.4%, 98.7%, and 97.6%, respectively, whereas, for gonorrhea in females the sensitivities for endocervical, vaginal, and urine samples were 100.0%, 100.0%, and 95.6%, respectively. [doi: 10.1128/JCM.03461-12]. This demonstrates a very high accuracy for the test under consideration in the current study. There is always the possibility of incongruent results between

the standard of care PCR test and the Cepheid RTAT. If this happens the study subject will be contacted and arrangements will be made to have the appropriate care provided.

The possible outcomes for test results are:

1. RTAT is negative and PCR is negative: no adjustment needs to be made to care of the subject.
2. RTAT is negative and the PCR is positive: if the patient was not treated empirically during the index visit, as usual care for the department, the patient will be contacted and arrangements made to provide appropriate care. This contact is made as part of the quality assurance program of the department. The study team will verify this contact was completed.
3. RTAT is positive and PCR is positive: no adjustment needed if the clinician treated the patient during the index visit. If the patient was not treated then the same process will occur as in scenario 2.
4. RTAT is positive and PCR is negative: if the subject was not treated during the index visit then they will be contacted by the study team to explain that two highly accurate tests gave different results. The patient will be offered the opportunity to return for treatment. If the subject was treated during the index visit then they will be contacted by the study team to explain that two highly accurate tests gave different results. As treatment was already given there would be no change to the management of the patient.

D. Subjects and Sampling

a. Inclusion Criteria
- Female patients age 18-55
- Signs or symptoms consistent with sexually transmitted infection
- Medical provider willing to consider the result of the rapid turnaround test in the decision to treat for gonorrhea/chlamydia
- Must have a urine specimen obtained and a pelvic exam performed as part of the anticipated standard of care evaluation
- Patient agrees to wait for results of RTAT testing, in the likelihood they are assigned that group.
- Provides informed consent

b. Exclusion Criteria
- Age < 18 or > 55
- Signs of systemic infection
- Patient in whom the provider is unwilling to consider the result of the rapid turnaround test
- Patient who reports being treated for either gonorrhea or chlamydia in the preceding 3 months
- Patients undergoing evaluation for sexual assault
- Patients that are known to be pregnant or express concern that they may be pregnant
- Incarcerated patients
- Students/Employees of the facility
- Presence of any other condition(s) that the investigator feels makes the patient unsuitable for study inclusion.

c. Informed Consent Process: Patients who meet study criteria will be consented prior to participation in any study related procedure. A copy of the consent form and privacy form

(HIPAA) will be provided and reviewed with the patient. This study will be voluntary and confidential. All study data with potential patient identifiable information will be kept in a locked office.

d. Study Location: Study will be conducted in the Adult Urgent Care Center at the University of Maryland Medical Center, which is managed by the Department of Emergency Medicine and in the Adult Emergency Department.
e. Potential Problems: Insufficient number of patients who meet all inclusion and exclusion criteria. Lack of eligible patients willing to participate in the study.

E. Data Collection and Objectives

Primary Outcomes:

- To evaluate the effect of utilizing a rapid turnaround GC/CT test on treatment of patients with possible STIs

Secondary Outcomes:

- To evaluate the effect of utilizing a rapid turnaround GC/CT test on length of stay in the Emergency Department
- To compare the congruence of test results between the rapid turnaround GC/CT test with the usual care test (send out PCR) in those subjects that have both performed (Experimental Group).
- To evaluate the effect of utilizing a rapid PCR test on healthcare costs.
- To evaluate patient satisfaction with the 2 diagnostic groups.
- To compare need for additional healthcare utilization between the groups.

F. Methods

Patients meeting eligibility criteria and who have signed the research informed consent will be enrolled in this study. The subject will be randomly assigned to either the control or the experimental group. We will utilize the online pre-randomization website: https://www.graphpad.com/quickcalcs/randomize1.cfm for randomization into one of the two groups. All subjects will be assigned a study participant number. Subject data collected will include demographic information, symptoms of the present illness and physical exam findings.

The control group will be followed according to standard of care as listed below in Question 2. The medical records will be reviewed following treatment and discharge to determine if this subject received empiric treatment.

The experimental group will be followed according to standard of care with the following additional research analysis: A cervical swab sample will be analyzed with the RTAT. The RTAT has been approved by the FDA for diagnosing suspected sexually transmitted infections (STIs).

For the experimental group, a study team member will verbally obtain the consent of the treating provider for the subject as to whether or not they would empirically treat the study subject if the RTAT was not being run. After results of the RTAT test are obtained the treating provider will be given the results. The treating provider can determine the course of treatment based on this test and their history of clinical exam findings. Subjects with negative RTAT results are not precluded from receiving treatment. If the result of the RTAT of the experimental group is

“invalid”, the subject will be treated according to usual care and, at the discretion of the provider. This may be to either empirically treat or wait to treat pending the results of the usual care tests. This process to either treat or withhold antibiotics for a suspected sexually transmitted infection (STI) until the culture results have returned is in accordance with the standard of care for the University of Maryland Medical System.

For both groups- 1) Additional data will be collected on length of stay in the Adult Emergency Department and Urgent Care Center. The time of interest is from when the subject first undergoes pelvic examination to the time that the subject leaves the treatment area.
2) A patient satisfaction survey to compare assigned treatment groups. 3) Telephone contact 1 to 2 weeks after enrollment. Using a standardized interview form they will be asked about resolution of symptoms, need for additional treatment, compliance with treatment, and satisfaction.

Subjects who have enrolled in the study and subsequently changed their mind about waiting for their results may choose to leave. All study participants who will be enrolled will undergo standard of care testing to evaluate for a STI. Per standard of care at the University of Maryland Medical System, they will be treated empirically or have antibiotics withheld at the discretion of the provider until the culture results have returned, after the subject has been discharged.

Regardless of the group assignment, any standard of care nucleic acid amplification tests that are positive; and the subject did not receive adequate antibiotics will be contacted (as per standard of care). These study subjects will be managed as part of usual care by the quality assurance (QA) program. These subjects may be asked to return to the emergency department for further evaluation, at the discretion of the study subject and QA resident, again as per standard of care.

The GeneXpert IV Device manufactured by Cepheid will be located in the Adult Emergency Department point-of-care (POC) laboratory area. Once we have CICERO approval, we will obtain a laboratory and POC approval to maintain the donated device in this area. RTAT performance will be done by members of the research team, trained using the materials made available by the manufacture.

Section 2: Procedures Already Being Performed for Diagnostic or Treatment Purposes

Females presenting to the Adult Emergency Department or Urgent Care Center will undergo the standard evaluation appropriate for suspected chlamydial or gonoccocal infections. As part of usual care, vitals signs will be measured, a physical exam will be performed and a urine specimen will be obtained for a urinalysis and a pregnancy test. A pelvic exam will be performed to collect endocervical samples for nucleic acid amplification analysis. This cervical swab is done for the purpose of diagnosis. The results of the cervical swab may take up to 2 days. This process to either treat or withhold antibiotics for a suspected sexually transmitted infection (STI) until the culture results have returned is in accordance with the standard of care for the University of Maryland Medical System. As shown previously, these patients are often started on empiric therapy that is not necessary based on the final results of testing.

Review of Literature:

In 2007, Newman et al. [doi: 10.1086/511422], gave an update discussing the management of Gonorrhea in the United States. It was discussed that *Neisseria gonorrhoeae* has the ability to develop antibiotic resistance. This paper discusses criteria for treating gonorrhea and how to treat gonorrhea at varying levels of antimicrobial resistance. Newman also discusses treatment options for patients that have adverse reactions to cephalosporins or quinolones.

In 2013, Tabrizi et al. [doi: 10.1128/JCM.00806-13], evaluated the sensitivity and specificity of the GeneXpert CT/NG in its ability to detect *Chlamydia trachomatis* and *Neisseria gonorrhoeae* compared to closely related bacterial species. In all isolates tested of both *N. gonorrhoeae*, the Xpert detected all isolates, and reported no false positives when testing other *Neisseria* species. Results were similar for *C. trachomatis*, Xpert correctly detected all 15 different serovars. This paper concludes that the GeneXpert CT/NG assay is highly sensitive and highly specific.

In 2013, Gaydos et. al. [doi: 10.1128/JCM.03461-12] completed a review of the Cepheid GeneXpert and its potential use in clinical settings. This review discussed how the short time interval required for the assay (90 minutes) might allow patients to be treated for CT/NG before leaving the clinic. This could in turn reduce the number of untreated patients who later may develop pelvic inflammatory disease. The review mentions how possible barriers to this could include patients refusing to wait the 90 minutes required for the assay. There may also be financial barriers to implementing this form of testing.

In 2014, the Center for Disease Control published its annual STD surveillance report. In this report, it was shown that infections with *Chlamydia trachomatis* and *Neisseria gonorrhoeae* are the most commonly reported sexually transmitted diseases in the United States, with 1,441,789 cases of chlamydia and 350,062 cases of gonorrhea in the US in 2014.

In 2014, Gaydos C. A [doi: 10.1586/14737159.2014.871495], reviewed the use of a new rapid real-time PCR, the Cepheid GeneXpert® (Xpert) CT/NG assay, for *Chlamydia trachomatis* and *Neisseria gonorrhoeae*. They found that the rapid, real time PCR nucleic acid amplification test demonstrated near-perfect sensitivity and specificity in urogenital specimens. Results are provided in approximately 90 minutes, and the Xpert has a platform for testing specimens directly from patients, with no hands-on manipulation from specimen loading to receiving results. This paper highlights the potential of the Xpert technology to change the diagnostic protocol in the clinical setting.

In 2015, Brook [doi:10.1136/sextrans-2014-051997] completed a study that evaluated the utility of point-of-care and rapid nucleic acid amplification techniques for the diagnosis of chlamydia and gonorrhea. It was found in the literature review that GeneXpert was better than other point-of-care tests with a sensitivity of 97.5%–98.7% and a specificity of 99.4%–99.9%. It also found that GeneXpert was the best for gonorrhea as well with a sensitivity of 96-100% and specificity of 99.9-100%. It was determined that using rapid NAAT alone could allow for a reduction in average time until treatment but only a small reduction in sensitivity/specificity.

In 2015, Holley et al. [doi: 10.1016/j.ajem.2015.06.009], examined the rates of overtreatment of CT and NG infections in the ED. This study found that the rate of overtreatment in the 2 inner-city EDs studied was 86%. Currently, there is no protocol that guides ED providers on when to treat patients in whom NG or CT infection is being considered, and presently providers will tend to treat patients empirically for both STDs without any objective data. This study cited the need for reexamination of the current protocol in evaluating possible CT/NG infection.

Reference List:

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