Evidence Based Practice for Management of Emerging Sexually Transmitted Infection, Mycoplasma Genitalium

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Abstract

This is an evidence-based practice (EPB) recommendation for management of Mycoplasma genitalium presented as a capstone project. It is a critical review analysis on the current data that is available on Mycoplasma genitalium to clinicians in the United States. The EBP data used for review and analysis was focused primarily on World Health Organization (WHO), Center for Disease Control and prevention (CDC) and clinical resource of UpToDate (CDC, 2021; Martin, 2021; WHO, 2021). The data in 2021 European sexually transmitted infection (STI) guidelines, British STI guidelines, Australian STI guidelines, and Canadian STI guidelines on Mycoplasma genitalium were also taken into consideration when developing the EBP recommendation presented in this paper (ASHM, 2018; Canada Mycoplasma genitalium, 2021; Jensen et al., 2021; Soni et al., 2019). The EBP recommendation put forth in this paper will allow a healthcare provider to safely and effectively recognize and manage Mycoplasma genitalium. It is crucial that a clinician be aware on how and when to diagnose and treat Mycoplasma genitalium due to its potential of becoming one of the first untreatable bacterial sexually transmitted infections in the United States (Moi et al., 2015; Unemo & Jensen, 2017).

Keywords: Mycoplasma genitalium, mgen, M. genitalium, M. gen, MG, genitalium, and/or Mycoplasma, mycoplasma genitalium guidelines, persistent urethritis, persistent cervicitis, non-gonococcal urethritis, STI guidelines, macrolide resistance, society guidelines and STI, CDC and mycoplasma genitalium,

Table of Contents

Chapter 1

Introduction and Background

Mycoplasma genitalium is a sexually transmitted infections (STI) that can now be easily tested for and treated by a primary care clinician. However, many providers are unaware of this newly emerging STI despite its discovery since the early 1980's (Jensen et al., 2021; Martin, 2021; Soni et al., 2019). Mycoplasma genitalium is a prokaryote, known to have the minimal amount of genetic material required to be considered one of the smallest self-replicating bacteria (Jensen et al, 2021; Martin, 2021; Taylor-Robinson & Jensen, 2011). Detection of Mycoplasma genitalium cannot be relied on via culture or gram stain (Martin, 2021; Soni et al., 2019; Taylor-Robinson & Jensen, 2011). Mycoplasma genitalium can take up to 4-6 months to grow in culture, and will not be visible in a gram stain related to the lack of a cell wall (Martin, 2021; Taylor-Robinson & Jensen, 2011). In January of 2019 the United States Food and Drug Administration (FDA) approved the first test that will assist clinicians in the detection of Mycoplasma genitalium known as the Aptima Mycoplasma genitalium Assay by the Hologic company (FDA, 2019). This new FDA approved test detects the presence of RNA of the bacteria Mycoplasma genitalium (Aptima, 2019). Mycoplasma genitalium can be found to inhabit both the urinary and genital tract (Aptima, 2019). The preferred specimen type to obtain the best results related to an increase in clinical sensitivity as indicated in the Aptima MG Assay package insert is the first void urine from males or a vaginal swab from females either self-collected or clinician collected (Aptima, 2019).

The transmission of Mycoplasma genitalium is direct genital to genital contact (Martin, 2021; Taylor-Robinson & Jensen, 2011). Mycoplasma genitalium is found most commonly in the epithelial cells of the urinary and genital tract, detected most commonly on vaginal, penile,

and rectal mucosa (CDC, 2021; Jensen et al., 2021; Martin, 2021; Taylor-Robinson & Jensen, 2011). The detection of Mycoplasma genitalium on oral mucosa has been detected, although it was significantly very low in oral detection (Jensen et al., 2021; Martin, 2021). Mycoplasma genitalium infections are usually symptomatic (CDC, 2021; Jensen et al., 2021; Martin, 2021). The signs and symptoms that are most commonly attributed to Mycoplasma genitalium, are very similar to those that are commonly associated with the non-gonococcal STI Chlamydia trachomatis (CDC, 2021; Jensen et al., 2021; Martin, 2021).

Signs and symptoms in the female population includes an increase in vaginal discharge, dysuria, postcoital bleeding, lower abdominal pain, and/or mucopurulent cervicitis/urethritis (CDC, 2021; Jensen et al., 2021; Martin, 2021). The signs and symptoms in the male population includes dysuria, urethral discharge, urethritis, proctitis, and/or balanitis (CDC, 2021; Jensen et al., 2021; Martin, 2021). Mycoplasma genitalium has been found to be the most common cause for recurrent or persistent nongonococcal urethritis, cervicitis and pelvic inflammatory infections (PID) (CDC, 2021; Jensen et al., 2021; Martin, 2021).

Complications that can be caused by the sexually transmitted infection from Mycoplasma genitalium in females are infertility, endometritis, salpingitis, pelvic inflammatory disease and sexually acquired reactive arthritis (Jensen et al., 2021; Martin, 2021). The complications that can be caused in males related to Mycoplasma genitalium infection are epididymitis, proctitis, orchitis, and sexually acquired reactive arthritis (Jensen et al., 2021; Martin, 2021). The Treatment of Mycoplasma genitalium in the United States is limited to only two FDA approved antibiotics, they are azithromycin and moxifloxacin (CDC, 2021; Martin, 2021).

Throughout this paper Mycoplasma genitalium may be referred to in the multiple ways it is published, which are: M. genitalium, Mgen, mgen, M. gen, MG and/or genitalium.

Identification of the Problem

Mycoplasma genitalium was recently introduced to US clinicians as a sexually transmitted infection in July 23, 2021 in the CDC's most recent published STI guidelines (CDC, 2021). Despite its novelty to the list of sexually transmitted infections, Mycoplasma genitalium has been found to be more prevalent than gonorrhea and almost as equal to, in the prevalence of chlamydia (Getman et al., 2016; Manhart et al., 2013; Martin 2021; Pond et al., 2014). A study that was conducted across multiple STI centers in the United States in 2016 with 946 participants, found that the prevalence of Mycoplasma genitalium was at to 16.3% in females and 17.2% in males in their subject population (Getman et al., 2016).

The problem identified is the lack of clear guidelines that clinicians in the United States have on testing and treating for Mycoplasma genitalium (CDC, 2021; Golden et al., 2017; Martin, 2021). It was not until the recent publications of STI guidelines from World Health Organization (WHO) and the CDC in July of this year (2021) that Mycoplasma genitalium was even recognized to be an STI (CDC, 2021; WHO, 2021). Other countries such as Australia, New Zealand and Europe have recognized Mycoplasma genitalium as an STI and have been monitoring, testing and treating for this STI in their population since 2016 (ASHM, 2018; Jensen et al., 2021; Spooner, 2017). Other than the lack of guidance, there is also a lack of consistency in the main bodies that give direction for Mycoplasma genitalium STI testing and treatment to a US clinician (CDC, 2021; Golden et al., 2017; Martin, 2021). The burden then lies on the practicing clinician to find the best and most effective way to screen, test and treat their patients for Mycoplasma genitalium that may affect their patient's reproductive health (CDC, 2021, Martin 2021). Below is a summarization of the CDC guidelines 2021, WHO guidelines 2021, UpToDate recommendations in 2021, 2021 European STI guidelines, British STI guidelines, and

Australian STI guidelines on their recommendation fort the management of Mycoplasma genitalium infections.

Synopsis of current guidelines/recommendations:

CDC guideline recommendations for Mycoplasma genitalium (CDC, 2021):

The CDC recommendation is to test for Mycoplasma genitalium only after treatment failure has occurred for urethritis, cervicitis, or pelvic inflammatory disease (PID). The treatment for M. gen is a 2-step approach using two different antibiotics. The first step after confirming the presence of M. gen with the use of FDA approved nucleic acid amplification test (NAAT), is to prescribe doxycycline 100 mg twice a day (BID) for 7 days. The second step is to then prescribe moxifloxacin 400mg once a day (QD) for 7 days. If moxifloxacin cannot be used, an alternative approach is to prescribe doxycycline 100 mg bid for 7 days, followed by azithromycin 2.5 grams extended treatment, with directions on prescription to take azithromycin 1 gram on day 1, then 500 mg on day 2-4. The treatment recommendation for PID caused by M. gen is moxifloxacin 400mg BID x 14 days. The CDC does endorse for clinicians to use a non-FDA approved lab test that can detect azithromycin resistance if it is available to them.

WHO recommendations June 2021 guidelines for symptomatic STI (WHO, 2021):

The WHO continues to recommend symptomatic empiric therapy that covers gonorrhea and chlamydia (G/C) for the symptom of urethral discharge. A new recommendation as of June 2021, is that if the test results are negative for G/C, then testing and treatment for Mycoplasma genitalium and Trichomonas vaginalis (TV) is recommended. The WHO recommends that Mycoplasma genitalium be considered as a possible culprit in persistent or recurrent symptoms of PID, vaginal discharge, cervicitis, and/or urethral discharge. The treatment recommendations for Mycoplasma genitalium are azithromycin 500mg on day 1, then 250 mg on day 2-5. The

WHO does not give any treatment recommendations for PID infection with Mycoplasma genitalium. A test of cure with a molecular assay such as NAAT is recommended to be repeated no earlier than 21 days after treatment.

UpToDate recommendations for M. genitalium infection (Martin, 2021):

The evidence-based point of care clinical resource known as UpToDate recommends Mycoplasma genitalium be tested when there is urethritis, cervicitis, or PID symptoms. It also recommends for partners of positive Mycoplasma genitalium patients to be tested for Mycoplasma genitalium. The recommendation advises to order a first void urine sample for males and vaginal swabs for females that are either clinician or self-collected. The recommendation is also to use the Mycoplasma genitalium NAAT that was cleared by FDA, and like the CDC it also endorses the use of the non-FDA Mycoplasma genitalium assays that detect macrolide resistance if they are available to clinicians. The treatment recommendation for a positive Mycoplasma genitalium is moxifloxacin 400mg by mouth once a day for 7 days. An alternative treatment is the high dose extended treatment regimen of 2.5 grams azithromycin, prescribing 1g on Day 1, then 500mg on Day 2-4. The recommendation for follow up is a test of cure at 2-3 weeks after treatment was initiated.

2021 European guideline on the management of Mycoplasma genitalium infection (Jensen et al., 2021):

The most recent European guidelines released in 2021 recommend testing all symptomatic patient with cervicitis, postcoital bleeding, dysuria of unknown etiology, urethritis, epididymitis, orchitis, proctitis for Mycoplasma genitalium. The recommendation is to use a nucleic acid amplification test (NAAT) with the capabilities of macrolide resistance detection. The treatment for uncomplicated M. gen infection that results to be macrolide sensitive is the

extended azithromycin 1.5 grams regimen, prescribing azithromycin 500 mg on day one, followed by 250 mg on day 2 to 5. Another alternative treatment is josamycin 500mg three times a day for 10 days (this medication is not an option in the United States). The treatment for an uncomplicated M. genitalium infection with detected macrolide resistance is moxifloxacin 400 mg once a day for 7 days. The recommended treatment for a complicated M. genitalium such as a diagnosis of epididymitis or pelvic inflammatory disease is moxifloxacin 400 mg once a day for 14 days. The third line treatment, which is reserved for persistent Mycoplasma genitalium infection after failed treatment with azithromycin and moxifloxacin is doxycycline or minocycline 100 mg twice a day for 14 days or pristinamycin 1gram four times a day for 10 days (this medication is not available in the United States). The European guidelines stress the importance of using resistance guided therapy to curtail the antimicrobial resistance to azithromycin and moxifloxacin in their STI Mycoplasma genitalium recommendations. A test of cure is recommended no earlier than three weeks after completion of treatment.

British Association for sexual health on mycoplasma genitalium 2018 guidelines (Soni et al., 2019):

The United Kingdom guidelines recommend testing for Mycoplasma genitalium infection with detection of macrolide resistant mutation in all symptomatic male/female patients and their partners. The preferred male specimen of choice is to use the first void urine and for females the preferred specimen of choice is a vaginal swab that is either self or clinician collected. The treatment recommendation for uncomplicated Mycoplasma genitalium infection is doxycycline 100 mg twice a day for seven days, followed by an extended treatment of 2 grams azithromycin, prescribing 1 gram on day one, then 500 mg on days two and three. If Mycoplasma genitalium macrolide resistance is detected, the treatment for uncomplicated M. gen infection is

moxifloxacin 400 mg once a day for 10 days. The treatment recommendation for a complicated M. gen infection such as with a PID is moxifloxacin 400 mg once a day for 14 days. An alternative treatment regimen for either complicated or uncomplicated M. gen infection is doxycycline or minocycline 100 mg twice a day for 14 days. The third line treatment recommendation is doxycycline 100 mg twice a day for seven days, followed by pristinamycin 1gram four times a day for 10 days (this medication is not available in the United States). The recommendation is a test of cure at three to five weeks after initiation of treatment.

Australian STI Management guidelines 2018: Mycoplasma genitalium (ASHM, 2018):

The Australia's' STI's management guideline recommend testing with NAAT for mycoplasma genitalium with macrolide resistant mutation detection on all symptomatic patients and their partners. The recommendation is to test the first void urine in males or a self or clinician collected vaginal swab in females. The treatment recommendation for Mycoplasma genitalium that is macrolide sensitive is doxycycline 100 mg twice a day for seven days, followed by extended treatment azithromycin 2.5 grams, prescribing 1 gram on day 1 followed by 500 mg on day two through four. The treatment recommendation for Mycoplasma genitalium macrolide resistant infections is doxycycline 100 mg twice a day for seven days followed by moxifloxacin 400 mg once a day for 7 days. For complicated Mycoplasma genitalium infections such as a diagnosis of PID, the recommended treatment is moxifloxacin 400 mg once a day for 14 days. A test of cure is recommended four weeks after starting therapy.

Chapter 2

Research Significance

Clinicians need to develop an awareness of Mycoplasma genitalium, especially with the availability of the first approved FDA test for its detection as of January 2019 (FDA, 2019). The establishment of an evidence-based recommendation on screening, testing, and treating for Mycoplasma genitalium will allow a clinician to increase surveillance in the US population and treat this STI appropriately (FDA, 2019). An evidence-based standard on Mycoplasma genitalium will also contribute to a provider's education and management on this novel STI. Lastly, an established evidence-based recommendation for Mycoplasma genitalium may assist in decreasing a pending health threat of antimicrobial resistance to Mycoplasma genitalium (ASHM, 2018; Jensen et al., 2021; Spooner, 2017).

Theoretical Framework

The theoretical model that will be used for this project proposal is Nola J Pender's "Health Promotion Model" also known as HPM (Figure 1.1) (Pender's Health Promotion Model, 2020; Sakraida, 2014). Pender notes that health promotion is defined as a behavior that will increase a patient's well-being (Pender's Health Promotion Model, 2020; Sakraida, 2014). Her model states that health is not merely an absence of disease, but is in a positive dynamic state (Pender's Health Promotion Model, 2020; Sakraida, 2014). The HPM integrates the importance of cognition in health changing behavior, and its basis is formulated using social learning theory (Pender's Health Promotion Model, 2020; Sakraida, 2014). The model is based on how personal influences can affect how an individual can change health behavior (Pender's Health Promotion Model, 2020; Sakraida, 2014). The model was actually revised from the original model that was constructed in 1996 (Pender's Health Promotion Model, 2020; Sakraida, 2014). The revised

changes include an addition of three variables that can influence a person's health promoting behavior, which include activity-related affect, a commitment to a plan of action, and lastly the immediate competing demand and preferences (Pender's Health Promotion Model, 2020; Sakraida, 2014).

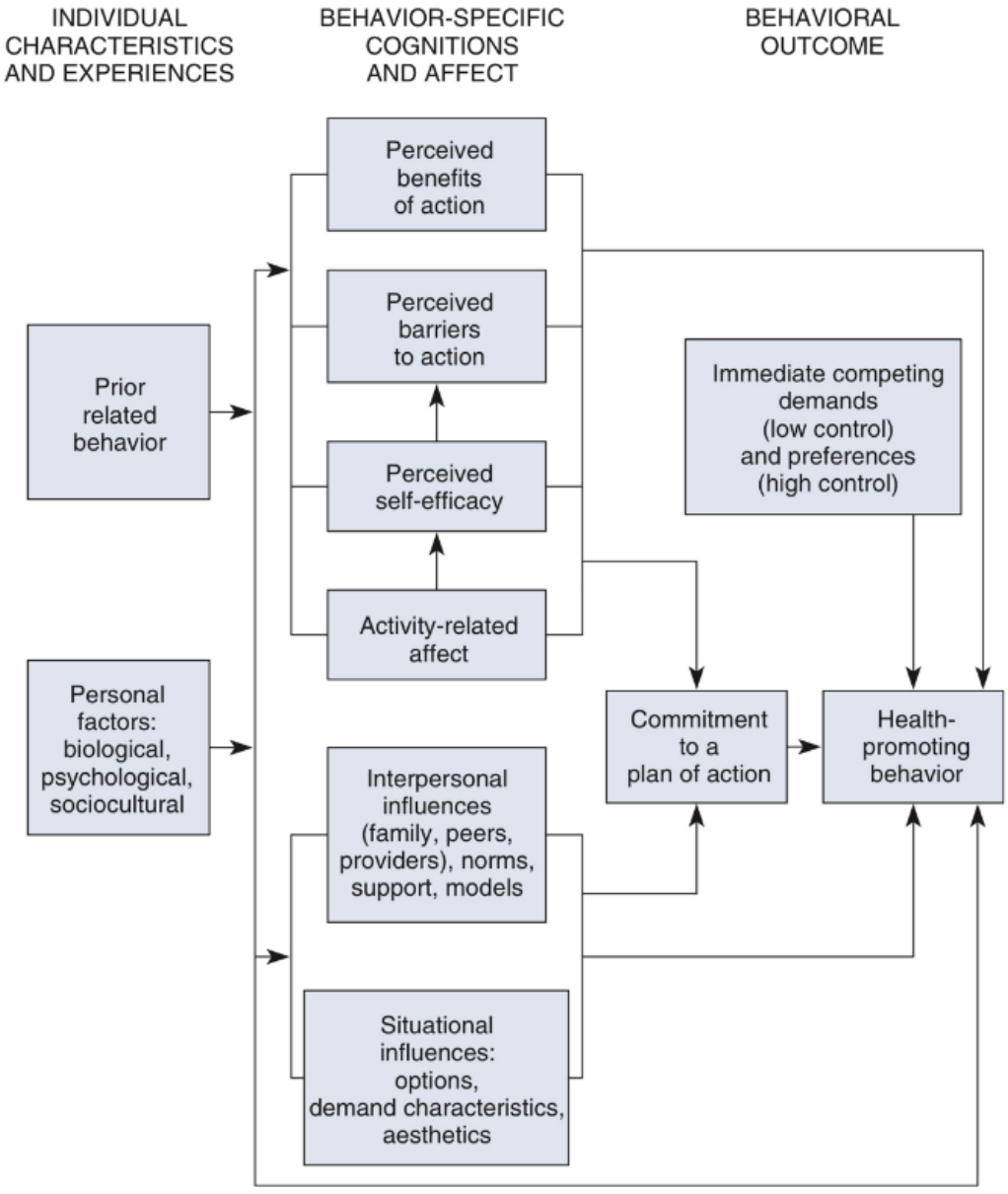

Figure 1.1 Obtained from Chapter 21 of Nursing Theorist and their work 8th edition (Sakraida, 2014).

This health promotion model was chosen because dealing with a new STI will require health promotion to not only patients, but healthcare practitioners as well. The CDC notes that sexually transmitted infections have been on the rise for the past six years (CDC, 2021). With the combination of an emerging STI known as Mycoplasma genitalium and its recent FDA approved test, a clinician will have the potential to increase the surveillance for prevalence and treat this rising STI (FDA, 2019; Golden et al., 2017). Standard practice for clinicians is to test for routine STI's of gonorrhea and chlamydia when a patient exhibits STI symptoms such urethritis, cervicitis, or pelvic inflammatory disease (CDC, 2021; Martin, 2021). After perceived benefits of actions are evaluated, a clinician may decide to add Mycoplasma genitalium when testing the symptomatic patient (Pender's Health Promotion Model, 2020; Sakraida, 2014). The perceived barrier to action for a clinician is going against the CDC recommendations of not testing for M. gen until antibiotic failure has occurred (CDC, 2021; Pender's Health Promotion Model, 2020; Sakraida, 2014). Lastly, the situational influences that can be addressed is the implementation of testing and treating for Mycoplasma genitalium using an evidence-based practice recommendation (Pender's Health Promotion Model, 2020; Sakraida, 2014). The clinical provider can change their behavior and perception on when to test and how to treat Mycoplasma genitalium (Pender's Health Promotion Model, 2020; Sakraida, 2014). The practitioner can see their actions of testing and treating for Mycoplasma genitalium as an "activity-related affect" (Pender's Health Promotion Model, 2020; Sakraida, 2014). The "perceived benefits of action" may contribute to what is known in the HPM as "commitment to a plan of action" (Pender's Health Promotion Model, 2020; Sakraida, 2014). Therefore, testing and treating for Mycoplasma genitalium leads to a health promoting behavior (Sakraida, 2014). With an evidence-based recommendation, a clinician will be better able to make an educated and

informed decision. These behavioral outcomes will not only positively affect their patient, but also their current practice and a potential public health threat (CDC, 2021; Martin, 2021; Pender's Health Promotion Model, 2020; Sakraida, 2014).

Purpose Statement

The purpose for the development of this evidence-based recommendation is to have a better understanding on screening, testing, and treating patients that come into the clinic with possible STI symptoms of Mycoplasma genitalium. There is currently a lack of consistent testing and treatment recommendations or guidelines for Mycoplasma genitalium (CDC, 2021; Martin, 2021). There is however an increasing antibiotic resistance developing against the two antibiotics available in the United States that are used to treat Mycoplasma genitalium (Bissessor, 2015; Dionne-Odom, 2018; Jernberg, 2008; Martin, 2021). The goal of this paper is to develop an evidence-based recommendation on testing and treating for Mycoplasma genitalium utilizing the most current data that is available at this time.

Chapter 3

Literature Review

Databases Used:

PubMed, Medline, Cochran's library, UpToDate, CDC, Society guideline links of STI management to include: WHO, Canadian, European, Australian, and British.

MeSH/KeyTerms:

Mycoplasma genitalium, mgen, M. genitalium, M. gen, MG, genitalium, and/or Mycoplasma, mycoplasma genitalium guidelines, persistent urethritis, persistent cervicitis, non-gonococcal urethritis, STI guidelines, mycoplasma genitalium treatments, mycoplasma genitalium and resistance, test/testing and mycoplasma genitalium, mycoplasma genitalium and diagnosing/diagnostics, mycoplasma genitalium detection, and/or macrolide resistance detection, mycoplasma genitalium and symptoms, mycoplasma genitalium and doxycycline, mycoplasma genitalium and moxifloxacin, mycoplasma genitalium and azithromycin, society guidelines and mycoplasma genitalium, society guidelines and STI, CDC and STI, CDC and mycoplasma genitalium, CDC and mycoplasma genitalium guidelines, STI Screening, mycoplasma genitalium and FDA approved, mycoplasma genitalium and FDA lab, cervicitis, FDA Mgen test azithromycin resistant, mycoplasma genitalium and US.

Method/Levels of Research Articles:

The method for evidence-based recommendation was a critical review of current literature on Mycoplasma genitalium guidelines and their references. A general search on PubMed for "Mycoplasma genitalium" was completed. A more focused search was then completed on current data for Mycoplasma genitalium from various society STI guideline links to include CDC, UpToDate, WHO, Canadian, European, Australian, and British STI guidelines

on mycoplasma genitalium (ASHM, 2018; Canada Mycoplasma genitalium, 2021; CDC, 2021; Jensen et al., 2021; Martin, 2021; Soni et al., 2018; WHO, 2021). References were then identified from these guidelines to focus on studies applicable to a practicing clinician in the United States. References on studies that solely contained medications not available in the United States such as pristinamycin, sitofloxacin, solithromycin, rifalazil, pivampicilin, and gatifloxacin were excluded from review. However, studies with at least one medication available in the United States were included. An inclusion criterion was that publications and abstracts were to be written or translated into the English language. Fifteen journal study articles were then identified for review and critique. The level of evidence of studies ranged between level 2 through level 4 (Lobiondo-Wood & Haber, 2017). There were twelve level 4 research articles critiqued, containing retrospective case studies, cohort clinical studies, longitudinal studies, or open treatment controlled clinical trials (Anagrius et al., 2013; Bissessor et al., 2015; Couldwell et al., 2013; Chernesky et al., 2017; Dionne-Odom et al., 2018; Durukan et al., 2020; Jernberg et al., 2008; Lusk et al., 2015; Piñeiro et al., 2019; Pond et al., 2014; Read et al., 2016, Read et al., 2019). There were two level 3 research articles critiqued which contained quasi-experimental and a randomized observational cohort (Bjornelius et al., 2008; Falk et al. 2015). Lastly, there was one level 2 research article critiqued which was a randomized controlled trial (Manhart et al., 2013).

Analysis of Studies/Journal Articles 1-15:

1)Treatment of mycoplasma genitalium. Observations from a Swedish STD clinic (Anagrius, C., Loré, B., & Jensen, J., 2013). Published in Journal Public Library of Science (PLOS) ONE, 8(4), e61481.

The objective of this observational cohort study was to evaluate treatment between doxycycline, azithromycin 1gram single dose, and azithromycin 1.5 grams extended treatment over 5 days. The design was set up as a non-experimental comparative retrospective case study within a nine-year time span. The study was conducted between 1998 and 2005, a long-term follow up was completed until 2009, and was finally published in 2013. Decreased generalizability was noted due to sampling bias of sample selection being a population attending one STI clinic in Sweden. The sample was well described, their method of selection was clearly defined. Sample size was relatively small having 185 women and 212 men for data collection The article did not identify its own possible threats to validity or reliability within the study. There may be some potential internal variability threat with instrumentation due to no identification on how specimens were stored or collected. There were no controls identified to account for any internal or external validity. There was no mention on reliability and validity of instruments or the tools that were used. The polymerase chain reaction (PCR) was the test used for presence or absence of Mycoplasma genitalium. There were statistics identified and the corresponding values were reported with the use of tables and figures that allowed for an easier interpretation of the results.

The study was compared the treatment of doxycycline, azithromycin 1gram single dose, and azithromycin 1.5 grams extended treatment regimen. There were no significant changes found between azithromycin 1gram single dose and the azithromycin 1.5 grams extended

treatment. A threatened validity and reliability in treatment outcomes was identified due to the smaller number of patients that were given the extended regimen of azithromycin 1.5 grams as a treatment. The treatment groups were as follows: 171 patients were given doxycycline, 117 patients were given azithromycin 1gram single dose, and only 26 patients were given the extended treatment of azithromycin 1.5 grams. The results showed that doxycycline had 43% cure rate, azithromycin 1gram single dose had 91% cure rate and azithromycin 1.5 grams extended treatment had a 96% cure rate. A secondary treatment of azithromycin 1.5 grams extended treatment was given to 52 patients of the 98 who failed doxycycline.

All 52 (100%) of those patients that received doxycycline followed by azithromycin 1.5 grams extended treatment had eradication of Mycoplasma genitalium. The study also observed for macrolide resistance from the failed patients that were treated with azithromycin 1gram single dose. The results showed that 7 out of 114 patients (3 samples were excluded from the initial 117) that received 1gram azithromycin developed macrolide resistance (6%). The study also found that 0% of patients treated with azithromycin1.5 grams extended dose developed macrolide resistance, which included the 52 patients that received it as a secondary treatment.

In conclusion the study confirmed the ineffectiveness of doxycycline to treat Mycoplasma genitalium. It also demonstrated that there was an associated risk for developing macrolide resistance with the 1gram single dose azithromycin versus the 1.5 grams azithromycin extended treatment. The comparison cannot be made directly between azithromycin 1gm single dose and the azithromycin 1.5 grams extended treatment, due to the initial significant smaller sample size of the azithromycin 1.5 grams extended treatment group. The study suggested that azithromycin 1gram single dose that is commonly used for nongonococcal urethritis/cervicitis may be increasing the macrolide resistance of Mycoplasma genitalium.

2) Antibiotic treatment of symptomatic Mycoplasma genitalium Infection in Scandinavia a controlled clinical trial (Bjornelius, E., Anagrius, C., Bojs, G., Carlberg, H., Johannisson, G., Johansson, E., Moi, H., Jensen, J. S., & Lidbrink, P., 2008). Published in Journal Sexually Transmitted Infections, 84(1), 72–76.

This was a quasi-experimental open treatment trial study that was based in an STI clinic located in Scandinavia between January 2002 to May 2004. The objective of this study was to evaluate the different treatment regimens of doxycycline and azithromycin in the eradication of Mycoplasma genitalium. The study evaluated primary treatment with doxycycline for 9 days versus azithromycin 1gm single dose. A secondary treatment was then evaluated with azithromycin 1.5 grams extended treatment over 5 days in those who failed doxycycline and doxycycline for 15 days in patients who failed azithromycin 1gram single dose. The sample was well described with sample bias identified as participants were a sample of convenience. The inclusion and exclusion criteria were clearly identified, and methods were clearly written and identified as well. A standardize protocol for obtaining medical history and clinical examination was utilized during the study. Labs were all completed in the same laboratory with the use of a PCR to identify Mycoplasma genitalium, which increased the reliability and validity. A decrease in threat to internal and external validity was recognized due to implementation of controlled variables in the laboratory setting. Fishers exact test two tailed to evaluate for proportional differences and Mann-Whitney test were used to evaluate differences between the gender and antibiotic groups. The results were based on a small sample size of 159 participants (115 male and 44 female). A decreased generalizability was noted due to sampling bias. The sample selection was done in an open treatment trial and the population being recruited was a sample of convenience from one STI clinic in Scandinavia. A significant number of participants

were given doxycycline treatment (65%) versus the azithromycin 1gram single dose (35%). The doxycycline in the male group had 17% effectiveness versus 85% effectiveness with azithromycin. In the female group doxycycline had a 37% effectiveness versus 88% effectiveness with azithromycin. The patients who failed the doxycycline trial then received azithromycin 1.5 grams extended treatment (500mg on day 1, then 250mg on day 2-5). The results for doxycycline followed by azithromycin 1.5 grams extended treatment was 96% effective in eradication of M. genitalium.

The study confirmed that doxycycline was ineffective in the eradication of Mycoplasma genitalium. It also confirmed that azithromycin 1.5 grams extended treatment of 500 mg on day 1, followed by 250 mg on day 2-5 should be considered as a first line treatment for M. genitalium in both genders. No results were given for secondary treatment with doxycycline because the sample was too small to document any of its results.

3) High prevalence of multidrug resistant Mycoplasma genitalium and human immunodeficiency virus infected men who have sex with men in Alabama (Dionne-Odom, J., Geisler, W. M., Aaron, K. J., Waites, K. B., Westfall, A. O., Pol, B. V., & Xiao, L., 2018). Published in Journal Infectious Diseases Society of America, 66, 796–798.

This was a sub-study from an STI study that was being conducted in an HIV primary care clinic located in Alabama. The purpose of this study was to evaluate the prevalence of Mycoplasma genitalium as well as the prevalence of macrolide resistance in a cohort between December 2014 to November 2016. The study consisted of 157 HIV-infected men with Mycoplasma genitalium infection. The inclusion criteria were identified clearly, participants needed to report receptive anal intercourse in the past month, 19 years or older, and have had no

antibiotic use within the past month. The detection of Mycoplasma genitalium and macrolide resistance, using a self-collected rectal swab and first catch urine were completed using a PCR assay. The control for internal reliability and validity procedures were described in detail. Appropriate statistical analysis was conducted such as Fisher exact test, Chi square for the categorical variables and nonparametric and one-way analysis for continuous variables with use of the Kruskal-Wallis test. A decrease generalizability is noted due to the sample being on a specific population on which the study was conducted. However, results may be generalized to the specific population of men who have sex with men (MSM) who are HIV positive. The study found prevalence of Mycoplasma genitalium infection to be at 17.2% urogenital and rectal sites. As opposed to chlamydia prevalence in the same population to be at 16.8% and gonorrhea prevalence at 7%. The detection of macrolide resistance in this study was found to be at 74.1%. The detection of fluoroquinolone resistance was found to be at 29.6% and the multidrug resistance where both mutations are concurrent was found to be at 24%.

This study was able to establish the high prevalence of Mycoplasma genitalium in this particular population of MSM. It also raised a concern of the high M. gen macrolide resistance that was already found to exist in this population. A further concern in the study was about the detection of fluoroquinolone resistance and the multidrug resistance that was also found to exist in this population.

4) Guided antibiotic therapy for Mycoplasma genitalium Infection: analysis of mutations associated with resistance to macrolides and fluoroquinolones (Piñeiro, L., Idigoras, P., de la Caba, I., López-Olaizola, M., & Cilla, G., 2019). Published in Journal Enfermedades Infecciosas y Microbiologia Clinica, 37(6), 394–397.

This study was a non-randomized, non-experimental clinical study of a cohort in Spain between 2014-2017. The sample selection in this study was well represented of the general population with a total sample size of 8,388 that was analyzed for Mycoplasma genitalium. The prevalence in the samples analyzed of Mycoplasma genitalium was found to be 4%. The samples were obtained from different areas in the medical community. Most of the samples (65%) were from primary care clinics, 21% were from gynecology clinics, 9% were from an STI Center, 3% were from emergency departments, and 2% were from a urology clinic. The objective was to evaluate the susceptibility of Mycoplasma genitalium to the current treatments available using a rapid probe-based PCR with results available in less than 24 hours. They evaluated the rapid commercial real time polymerase chain reaction (PCR) technique with the conventional PCR assay that typically takes approximately three or four days. The study had clear internal controls for reliability and validity, and it provided tables that supplemented text well, with good information presented.

The study found that macrolide resistance was detected in approximately 16.3% of the samples, with greater resistance noted in the men who have sex with men (MSM) group (32.5%). It was also observed that 60% of the resistant strains were detected in the patients that had a prior history of azithromycin treatment, as compared to only 7.4% of the patients who did not have prior azithromycin treatment. This study also confirmed that 1gram azithromycin single dose had a higher rate of macrolide resistance (31.3%) when compared to the extended regimen of

azithromycin (7%). This study was able to demonstrate how the use of Mycoplasma genitalium rapid technique can assist clinicians in the guided treatment of Mycoplasma genitalium.

5) Macrolide resistance and Azithromycin failure in a Mycoplasma genitalium – infected cohort and response of azithromycin failures to alternative antibiotic regimens (Bissessor, M., Tabrizi, S. N., Twin, J., Abdo, H., Fairley, C. K., Chen, M. Y., Vodstrcil, L. A., Jensen, J. S., Hocking, J. S., Garland, S. M., & Bradshaw, C. S., 2015). Published in Journal Clinical Infectious Diseases, 60(8), 1228–1236.

This was a prospective study, also known as longitudinal cohort of non-randomized subjects based in Australia between July 2012 and June 2013. The purpose of this study was to determine the efficacy of alternative antibiotic regimens other than 1gram azithromycin, such as moxifloxacin and pristinamycin for the treatment of Mycoplasma genitalium. The study also aimed to evaluate the continued effectiveness of 1gram azithromycin for Mycoplasma genitalium. Methods were well described, appropriate analysis were completed to include Fisher exact tests, multi variable logistic regression analysis, and linear regression to determine Mycoplasma genitalium load differences between pre and post treatment of macrolide resistant mutation (MRM). Effective tables and figures were included in the study article. Detailed description on procedures for laboratory methods were discussed. There was sample bias related to the small sample of convenience from participants in an STI clinic from Australia. The sample size was a total of 155 participants. The majority of the participants were males (112/155) and most were symptomatic (107/112). There were some female participants (43/155) and most were asymptomatic, but were tested because they were in contact with a positive

Mycoplasma genitalium partner (25/43). Internal reliability and validity sample were compromised related to the sample being majority symptomatic male population.

The results showed that 1gram azithromycin effectiveness continues to decline (61% effectiveness) and increasing macrolide resistant mutation continues to increase in prevalence with its use (11%). The macrolide resistant prevalence in pre-treated participants was found to be 36%. The moxifloxacin treatment group demonstrated an 88% effective cure rate, with only 7 failures in which multi drug resistant mutations were detected to both azithromycin and fluoroquinolone. The treatment given to the multidrug resistant patients was pristinamycin taken 4 times a day for 10 days, had a 100% effective cure rate. The study evaluated a test of cure at 14 days post initial treatment and then again at 28 days. The results found that a test of cure can be performed at 14 days. This study continued to establish the possibility of multi-drug resistant strains becoming more prevalent and more difficult to treat, prompting clinicians to start using guided therapies if available rather than an empiric therapy approach.

6) *Failure of moxifloxacin treatment in Mycoplasma genitalium infections due to macrolide and fluoroquinolone resistance (Couldwell, D. L., Tagg, K. A., Jeoffreys, N. J., & Gilbert, G. L., 2013). Published in Journal International Journal of STD & AIDS, 24(10), 822–828.*

This study was a non-experimental case study, based on a cohort in an STI clinic from Australia between February 2008 to November 2011. The objective of this study was to find out if there was an association between macrolide resistance development related to a prior history of azithromycin 1gram single dose treatment. The sample size was 400 patients with non-gonococcal urethritis (NGU), 137 of them were tested for Mycoplasma genitalium. The results showed 53 out of 137 were positive for Mycoplasma genitalium, giving a prevalence of 39% in

the NGU population that was tested. This was a sub-study and information on data collection, instruments, methods, & procedures were not explained in this study, therefore reliability and validity were unable to be evaluated. There is a threat to internal and external validity and reliability related to the loss of study subjects. Out of the 53 positive Mycoplasma genitalium samples, only 32 patients were left as study subjects, the rest had missing samples. There is also sample bias due to the small sample size and the sample selection of convenience from an original study decreasing generalizability. There were macrolide resistance mutations in 47% of patients who had a history of azithromycin 1gram single dose. The study also showed the azithromycin cure rate in the small sample to be only 47%. In a small sample of 32 subjects, 6 of them (19%) showed fluoroquinolone resistance with no prior history of fluoroquinolone treatment.

The results confirm that azithromycin 1gram treatment history did in fact have a strong association with macrolide resistant mutation. The study also concluded that there is a decrease effectiveness of azithromycin to Mycoplasma genitalium and an increasing prevalence of fluoroquinolone resistance. These findings are a bit concerning due to the fact that the United States only has macrolide azithromycin and fluoroquinolone moxifloxacin as a treatment for STI of Mycoplasma genitalium.

7) *Mycoplasma genitalium antibiotic resistance - mediating mutations in Canadian women with or without Chlamydia trachomatis infection (Chernesky, M. A., Jang, D., Martin, I., Hoang, L. M., Naidu, P., Levett, P. N., Wylie, J., Rebbapragada, A., Ratnam, S., Smieja, M., Weinbaum, B., & Getman, D., 2017). Published in Journal Sexually Transmitted Diseases, 44(7), 433–435.*

This was a retrospective, non-experimental cohort study based in four Canadian provinces in 4 different STI clinics. The objective of this study was to determine Mycoplasma genitlaium prevalence and mutations of antibiotic resistance in the Canadian provinces. It also studied if detection of Mycoplasma genitalium had an association with a positive chlamydia. The samples studied were remnants from positive chlamydial tests in four different Canadian provinces. There was adequate reliability and validity, using controls and matching, as well as using the same laboratory. They used a control group that had woman who were negative for Chlamydia during the same time frame. The inclusion criteria were discussed in detail, stated it included 15 to 58 eight years old woman with a Chlamydia positive test. Re-testing was completed for confirmatory testing and there were control samples during testing. There were some internal and external variables that may threaten validity and reliability such as samples used were remnant samples. It is unknown how study samples were collected, stored or shipped. It is also unknown how the specimens were maintained and preserved during transport. The article indicated prevalence ratios and chi-square statistics which were demonstrated tables and test results provided. The limitations are that it is a very specific population, since inclusions were only woman who attended STI clinics and were positive with chlamydia. There was a decreased generalizability noted due to sample selection of convenience and the specific population of female positive chlamydia subjects within a sample size of 985. The summary of results are as follows: there were 55 out of 75 positives for Mycoplasma genitalium in patients

that were also positive for Chlamydia (73.3%). Out of the positive Mycoplasma genitalium samples, there were 47.3% that were showing mutations to the 23S rRNA, which is strongly associated with macrolide resistance. Only 1.9% of the patients were fluoroquinolone resistant.

In conclusion Chlamydia and Mycoplasma genitalium are strongly associated to be co-infected in the patients identified. There is a substantial Mycoplasma genitalium macrolide resistant mutation noted in the Canadian population that was studied (47.3%).

8) *Cervicitis aetiology and case definition: a study in Australian women attending sexually transmitted infection clinics (Lusk, M., Garden, F. L., Rawlinson, W. D., Naing, Z. W., Cumming, R. G., & Konecny, P., 2015). Published in Journal Sexually Transmitted Infections, 92(3), 175–181.*

This was a cross-sectional cohort study based in Australia in three different STI clinics between 2006 through 2010. The objective of this study was to evaluate an outline of STI's associated with cervicitis and to suggest a definition that best describes cervicitis. The study examined three definitions of cervicitis and wanted to see which definition would best assist in diagnosing an STI. The three case definitions consisted of a symptomatic definition of cervical discharge to include yellow or a mucopurulent discharge, a microscopy definition where there is >30 polymorphonuclear leukocytes per high power field (pnml/hpf) also known as a cervical gram stain, and lastly a combination of both microscopy plus symptoms of cervical discharge. The procedures, laboratory and protocols used were very well described. There was adequate interrater reliability since all clinicians had standardized training for the techniques that were used throughout the study. There was good validity and reliability for cervical gram stain visualized by clinicians due to a control variable of having a laboratory scientist assess the same

samples. This was a large study with sample size of 558 woman. There was sample bias related to sample of convenience and the need for women to agree to a clinician obtaining the specimens rather than self-collected swabs. Three swabs were obtained during the study. The first swab was to assess for the cervical Gram stain, the second swab was to assess for a PCR for chlamydia and gonorrhea, and the third swab was to assess for a PCR Mycoplasma genitalium. There was a possible threat to internal validity and reliability of testing outcomes related to the collection method. Collecting three different specimens, and having Mycoplasma genitalium being the last one, may have contributed to having a less accurate representation of sample for Mycoplasma genitalium on the 3rd swab specimen. Since taking three different samples can lead to decreasing specimen sample of mucus and cells after each subsequent swab.

The study concluded that cervicitis is best described as cervical discharge with or without microscopic evidence. It also concluded that the microscopic symptom of > 30pnml/hpf should not be used alone to rule out a possible STI. The results of STI prevalence in the study associated with cervicitis was Chlamydia at 5.8%, Mycoplasma genitalium at 3.8%, and Gonorrhea at 1.1%. Lastly, the study confirmed that condom use does decrease risk of cervicitis.

9) *Resistance guided antimicrobial therapy using Doxycycline, Moxifloxacin, and Doxycycline-2.5G Azithromycin for the Treatment of Mycoplasma genitalium infection: efficacy and tolerability (Durukan, D., Read, T. H., Murray, G., Doyle, M., Chow, E. F., Vodstrcil, L. A., Fairley, C. K., Aguirre, I., Mokany, E., Tan, L. Y., Chen, M. Y., & Bradshaw, C. S., 2020). Published in Journal Clinical Infectious Diseases, 71(6), 1461–1468.*

The is a non-experimental, longitudinal cohort study using a prospective clinical evaluation in an STI clinic located in Australia between April 2017 and June 2018. The aim of

this study was to determine the effectiveness and tolerability of resistant guided therapy (RGT). There was an evaluation of treatment with doxycycline followed by azithromycin 2.5 grams extended treatment regimen in macrolide sensitive Mycoplasma genitalium. The macrolide resistant Mycoplasma genitalium treatment was doxycycline followed by moxifloxacin. The purpose was to evaluate and assess the adherence and tolerability to the combination therapy, and look for any new macrolide resistance following the azithromycin 2.5 grams extended treatment regimen. The sample size was 383, with a threat to internal and external validity related to maturation of the sample. A sample bias was occurred because it was a sample of convenience of patients attending an STI clinic. The sample distribution was as follows: there was 81 females, 106 males and 196 men who have sex with men (MSM). Methods, Procedures, data collection, and instruments were discussed in detail and they noted the use of ResistancePlus MG Assay by SpeeDx. Presumptive non-gonococcal urethritis (NGU) diagnosed patients were prescribed doxycycline. If a positive Mycoplasma genitalium was noted then the patients were requested to return and were prescribed a second antibiotic depending on the macrolide sensitivity. If Mycoplasma genitalium was macrolide sensitive they were prescribed azithromycin 2.5 grams extended treatment (1gram on day 1, then 500 milligrams day 2 to 4). If Mycoplasma genitalium macrolide resistant was detected the treatment was moxifloxacin 400 mg once a day for 7 days. A follow up test of cure approximately two weeks to one month after treatment was completed. There was adequate reliability and validity in the instrument used in the study. The ResistancePlus MG Assay reliability and validity was verified by retesting same samples using the gold standard sequencing PCR, only one patient was misdiagnosed. For analysis the article was rich in data and discussed univariable logistic regression and provided confidence intervals and prevalence ratios. However, no inferential statistics were used to

evaluate level of variability between groups, such as Fisher exact or chi-square. The results showed that macrolide resistant Mycoplasma genitalium was highest among MSM (men who have sex with men) approximately 83.7% compared to both heterosexual males and females at 58.8%. In total there were 274 patients considered to be macrolide resistant, which is 71.5% and 109 were macrolide susceptible which is 28.5%. The macrolide resistant Mycoplasma genitalium group, received treatment regimen of doxycycline followed by moxifloxacin, it demonstrated a cure rate of 92%, which had an 8% failure rate. The Mycoplasma genitalium macrolide sensitive group received treatment regimen of doxycycline followed by extended azithromycin 2.5 grams, it demonstrated a cure rate of 95.4%, which had a failure of 4.6%. The development of new post-treatment macrolide resistant Mycoplasma genitalium was 5 out of the 5 cases who failed the doxycycline-azithromycin treatment.

In conclusion, both regimens had high adherence and were well tolerated with minimal side effects. The study provided moderate evidence to suggest that this resistance guided antimicrobial therapy regimen could be used with an effective cure rate of 92%-95.4%. The results in this study did not demonstrate a decrease in macrolide resistance with the use of extended azithromycin treatment. The results did demonstrate the need for developing new medications or treatment regimens to treat Mycoplasma genitalium with the rising development of macrolide resistance detected in this study. The study also demonstrated that testing for macrolide resistant mutations will decrease the need for empiric treatment and the development of an FDA approved Mycoplasma genitalium macrolide sensitivity test will assist clinicians in resistant guided therapy.

10) *Azithromycin 1.5G over five days compared to 1g single dose in urethral Mycoplasma genitalium: impact on treatment outcome and resistance (Read, T. H., Fairley, C. K., Tabrizi, S. N., Bissessor, M., Vodstrcil, L., Chow, E. F., Grant, M., Danielewski, J., Garland, S. M., Hocking, J. S., Chen, M. Y., & Bradshaw, C. S., 2016). Published in Journal Clinical Infectious Diseases, 64(3), 250–256.*

This was a retrospective longitudinal cohort non-experimental case study. The objective of this study was to evaluate an extended azithromycin regimen of 1.5 grams over five days compared to the azithromycin 1gram in a single dose. The study also aimed to evaluate development of pre and post treatment macrolide resistance mutations and compared both regimens. However, the treatments were not compared during same time period. The azithromycin 1.5 grams extended treatment cases were evaluated between 2013-2015, while azithromycin 1gram single dose treatment cases were evaluated between 2012 through 2013. The data were extracted from the database of the STI clinic. The clinic had approximately 1500 NGU male cases per year. The sample size was 106 males, so it is not generalizable due to sample bias with selection of convenience and characteristics of the participants. Statistical analysis and methods were discussed in detail. There are some internal and external validity and reliability threats due to the retrospective data collection study and comparison of groups were not in the same cohort. The laboratory methods had good reliability and validity, especially with the use of the gold standard of sanger sequencing being used for macrolide resistant mutation detection.

The results did not demonstrate a significant difference in the cure rate between azithromycin 1gram single dose (52%) versus the extended regimen azithromycin 1.5 grams over five day (58%). The prevalence of macrolide resistant mutations in the samples between 2013

through 2015 (52%) versus 2012 through 2013 (44%) were comparable when the analysis was reviewed. There was an increase in prevalence of Mycoplasma genitalium that was noted in the 2013 through 2015 in the men having sex with men (MSM) population increasing from 53% to 76%. The study noted a higher cure rate when there was a lower Mycoplasma genitalium bacterial load. However, when a comparable analysis was conducted, they found that bacterial load was not a significant predictor of treatment outcome with a p - value of 0.06. The study did not find any significant difference in the development of macrolide resistant mutations between the 1.5 grams extended azithromycin regimen (12%) versus the 1gram azithromycin single dose regimen (18%). The study also concluded that MSM had a high association with macrolide resistance pre-treatment (76%) and failure with azithromycin treatment with only a 34% cure rate.

11) *Standard treatment regimens for nongonococcal urethritis have similar but declining cure rates: a randomized controlled trial (Manhart, L. E., Gillespie, C. W., Lowens, M., Khosropour, C. M., Colombara, D. V., Golden, M. R., Hakhu, N. R., Thomas, K. K., Hughes, J. P., Jensen, N. L., & Totten, P. A., 2013). Published in Journal Clinical Infectious Diseases, 56(7), 934–942.*

This was a randomized, controlled, double blinded, parallel group superiority trial (detects differences in group) study based in an STI clinic in Washington, between 2007 and 2011. The objective of this study was to evaluate the treatment effectiveness for NGU of azithromycin versus doxycycline. There was sample bias related to a purposive sample with criteria selection of subjects being symptomatic males for urethritis. The study sample size was 606 men randomly assigned to the azithromycin (304 participants) group or the doxycycline (302 participants) group. The treatment was either an active azithromycin 1gram single dose taken in

front of the clinician and a placebo doxycycline 100mg twice a day for 7 days or a placebo azithromycin 1gram single dose taken in front of the clinician and active doxycycline 100mg twice a day for 7 days. Neither the patients, nor the clinicians were aware of what medication was active in the primary treatment. There was a threat to internal and external validity related to a 30% (184/606) mortality related to loss of subjects to follow up. Another threat to internal validity was the order in which samples were collected. The sample types that were collected were both urine and urethral swabs. However, it did not state whether it was a first void urine or if urethral swabs were obtained prior to a urine specimen sample. There was a test of cure approximately three weeks after treatment was initiated, with a window time frame between 2 to 5 weeks. If patient symptoms persisted after completing the primary treatment, they would get the treatment that they did not receive the first time. Protocol modifications were completed during the study due to the low cure rate in the alternative therapy of either doxycycline or azithromycin. The protocol study changed to prescribe moxifloxacin 400mg by mouth once a day for 7 days if the patient returned with persistent symptoms after the primary treatment of either azithromycin or doxycycline.

The results indicated that there were no significant differences between azithromycin and doxycycline treatment for Mycoplasma genitalium. There was a low cure rate in both azithromycin (63%) and doxycycline (48%) for Mycoplasma genitalium. The microbiological cure rate of M. genitalium was even lower, at 40% with azithromycin versus 30% with doxycycline. The study concluded that both azithromycin and doxycycline were ineffective in the clinical and microbiological cure rate for Mycoplasma genitalium. There was a prevalence of Chlamydia at 24% and Mycoplasma genitalium at 13% in this sample of 606 symptomatic male population for urethritis.

12) Time to eradication of mycoplasma genitalium after antibiotic treatment in men and women (Falk, L., Enger, M., & Jensen, J., 2015*). Published in Journal of Antimicrobial Chemotherapy, 70* (11), 3134–3140.

This was a prospective longitudinal cohort observational study between 2010 to 2014 based in a Sweden STI clinic. There was selection bias due to a sample of convenience from STI clinic. The sample size was 90 with 44 males and 46 females. This study had two objectives. One objective was to evaluate the best time to complete a test of cure for Mycoplasma genitalium. The second objective the development of antibiotic resistance. Patients were randomized into two different treatment groups. The details of how they separated the groups was unclear, however a flowchart for delegation to the antibiotic groups was provided. There was good reliability & validity since the same lab was used for all specimens. There is a possible Internal and external validity threat related to fatigue bias since patients collected their own specimens' 12 times within a 26day time frame. There is also a threat of internal validity related to reporting bias since patients were to report any condomless intercourse throughout the study.

Results of the study demonstrated that the azithromycin 1.5 grams extended regimen produced a negative test within three days. The 1gram single dose of azithromycin produced a negative test in eight days. The moxifloxacin group achieved a negative test in three days. Doxycycline had a significant decreased cure rate of 37%, and achieved a negative test within one week. There was no significant difference in the time it took to get a negative lab result between 1gram azithromycin single dose and the extended azithromycin 1.5 grams regimen. The results of the antimicrobial cure rate were as follows: moxifloxacin had 80% (4/5); azithromycin 1gram single dose had 60% (9/15); azithromycin 1.5 grams extended treatment had

75% (47/62) and doxycycline only had 37% (3/8). There was macrolide resistance development in two women treated with azithromycin 1.5 grams extended regimen and in one woman treated with azithromycin 1gram single dose. The study concluded that there were no differences between the pre-treatment samples of bacterial load and the clearing of the infection or developing macrolide resistance. The study also concluded that a test of cure can be assessed at 3 to 4 weeks after treatment initiation. In conclusion the author highly recommended a test of cure at 3-4 weeks after treatment with azithromycin, if macrolide resistant mutations are not being routinely confirmed.

13) *High prevalence of antibiotic resistant Mycoplasma genitalium in nongonococcal Urethritis: The need for routine testing and the inadequacy of current treatment options (Pond, M. J., Nori, A. V., Witney, A. A., Lopeman, R. C., Butcher, P. D., & Sadiq, S. T., 2014). Published in Journal Clinical Infectious Diseases, 58(5), 631–637.*

This was an observational cohort study between September 2011 to December 2011 based in a genitourinary medical clinic in London. The sample size was 217 males. Sample bias was noted due to a sample of convenience and with the majority of the subjects being heterosexual males 199/217 (92%) and MSM 18/217. The objective of study was to evaluate the prevalence of Mycoplasma genitalium in comparison to gonorrhea, chlamydia, and trichomonas. It also focused on the Mycoplasma genitalium macrolide and fluoroquinolone resistance mutation. The study participants were symptomatic men with urethritis. Urethral smears and first void urine were used as samples in the study. The urine was used to test for chlamydia and gonorrhea and the residual of the sample was used to test for M. genitalium and trichomonas.

The procedures, methods, and instruments were well described with supplementary data for protocols included within the article.

The study results demonstrated a Mycoplasma genitalium prevalence of 4.7% (5/107) in asymptomatic subjects that were in the control group. They also noted that Gonorrhea and Chlamydia both had a prevalence of 1.9% (2/107), and Trichomonas had a prevalence of 0% in the control group. For symptomatic urethritis patients, Mycoplasma genitalium had a prevalence of 15.5% (17/110) equivalent to Chlamydia in this study which was at 15.6% (17/109). The prevalence of Gonorrhea was at 6.4% (7/109) and Trichomonas was at 1.8% (2/110). When only nongonococcal urethritis was taken into account, Mycoplasma genitalium had a higher prevalence than chlamydia at 16.7% versus 14.7% respectively. In the positive Mycoplasma genitalium sample population, 41% had a macrolide resistance mutation and 4.5% had fluoroquinolone resistance detected.

In conclusion this study recommended that symptomatic urethritis and cervicitis should be tested for Mycoplasma genitalium, especially since the prevalence was found to match that as being equivalent to Chlamydia. The study also demonstrated the need for development of a new or different antibiotic regimen that will be effective against Mycoplasma genitalium infection. The increased detection of both macrolide and fluoroquinolone resistant mutations is concerning.

14) *Azithromycin and Moxifloxacin for microbiological cure of Mycoplasma genitalium Infection: an open study (Jernberg, E., Moghaddam, A., & Moi, H., 2008). Published in Journal International Journal of STD & AIDS, 19(10), 676–679.*

Jernberg et al.

This study was a retrospective cohort survey between May of 2005 to December 2006 based in Norway. A large number of 10,109 samples were analyzed for Mycoplasma genitalium, 452 of them were positive, making the prevalence of M. gen at 4.5% in the study sample. The study objective was to evaluate whether azithromycin was in fact less effective in a population that was routinely given azithromycin 1gram for NGU, which such is the case in Norway. The treatments evaluated were azithromycin 1gram single dose, azithromycin 1.5 grams extended treatment over 5 days, ofloxacin 200mg twice a day for 10 days, and moxifloxacin 400mg once a day for seven days. Follow up was determined with a test of cure at 4 to 5 weeks. Threats to internal and external validity related to high loss, with 17% to 22% of the sample not returning for a test of cure. There was a good control because they only used one laboratory setting and only used PCR for testing samples. The effectiveness of the antibiotics were as follows: the 1gram single dose azithromycin was 79%; azithromycin 1.5 grams extended treatment was 78%; ofloxacin was 44% as primary treatment and 58% as a 2nd or 3rd line treatment. Lastly moxifloxacin had an effectiveness of 100% effectiveness on treating Mycoplasma genitalium. The hypothesis was supported through the data in that Norway, who used 1gram azithromycin for routine NGU treatment had a lower effectiveness of azithromycin in their population when compared to Sweden who uses doxycycline for their routine NGU treatment. The study also found that treatment between 1gram azithromycin vs extended 1.5 grams over five days had

similar effectiveness. Lastly, the conclusion was that moxifloxacin should be used if recurrent urethritis is seen in the clinic and there is no access to M. genitalium testing.

15) *Outcomes of resistance-guided sequential treatment of Mycoplasma genitalium infections: a prospective evaluation (Read, T. H., Fairley, C. K., Murray, G. L., Jensen, J. S., Danielewski, J., Worthington, K., Doyle, M., Mokany, E., Tan, L., Chow, E. F., Garland, S. M., & Bradshaw, C. S., 2019). Published in Journal Clinical Infectious Diseases, 68(4), 554–560.*

This study had a prospective evaluation cohort design which collected data between June 2016 to May 2017 in an STI clinic based in Australia. The objective of the study was to evaluate sequential treatment following doxycycline. The use of resistance guided test results determined a secondary treatment of azithromycin 2.5 grams extended treatment or sitafloxacin 100mg twice a day for 7 days. There was bias because it was a sample of convenience and there was only a small sample size of 244 participants. The participants were positive for Mycoplasma genitalium and the distribution was as follows: there were 52 women (21%), 68 heterosexual men (28%), and 124 MSM (51%). Bias occurs with the MSM since they represent more than half of the participants. Doxycycline did appear to decrease bacterial load by 2.6 $\log_{10.}$ However, it did not prevent macrolide resistance from occurring in the azithromycin 2.5 grams extended treatment group. There was macrolide resistance mutation post-treatment that occurred in 2.6% of participants. There were threats to internal and external validity, due to loss of participants from the original 429 positive mycoplasma infected patients. The study had approximately 56% of positive Mycoplasma genitalium infected patients during the study period in the STI clinic. Bacterial load of Mycoplasma genitalium was evaluated in only a portion (56 men) of the study participants. The study results indicated that there was Mycoplasma genitalium bacterial load

reduction in 50% (28/56) of the participants and an increase in 11% (6/56) of participants. The study did assess for adverse reactions on sequential therapy and demonstrated minimal side effects, the majority of side effects being nausea and diarrhea. Sitafloxacin, which is a fluoroquinolone had the least amount of side effects and was reported to have the highest adherence in completing the antibiotic treatment. The results of the sequential antibiotic therapy effectiveness were as follows: doxycycline followed by azithromycin 2.5 grams extended treatment had 94.8% and doxycycline followed by sitafloxacin had 92.2%. Lastly, the limitations noted for this study were that of reporting bias, since patient sexual practices during or after the treatment, but before the test of cure which can affect outcome of the study. Another limitation that was noted in this study was the possibility of funding bias, since SpeeDx is the company of the test used for detection of macrolide resistance (ResistancePlus MG) provides research funding for the STI clinic that this study was conducted.

Chapter 4

Literature Synthesis

The literature review shows consistent evidence that doxycycline is ineffective in the treatment a Mycoplasma genitalium (Anagrius et al., 2013; Bjornelius et al., 2008; Falk et al., 2015; Manhart et al., 2013). Six studies found that prior treatment with azithromycin 1gram single dose was highly associated with an increased risk of macrolide resistant mutations seen in Mycoplasma genitalium (Anagrius et al., 2013; Bjornelius et al., 2008; Couldwell et al., 2013; Jernberg et al., 2008; Manhart et al., 2013; Piñeiro et al., 2019).

However, there is also conflicting evidence that an extended azithromycin regimen would decrease macrolide resistant mutations (Anagrius et al., 2013; Bjornelius et al., 2008; Durukan et al., 2020; Falk et al., 2015; Read et al., 2016; Read et al., 2019). There were 4 studies that showed persistent macrolide resistant mutations despite using azithromycin extended treatment regimen (Anagrius et al., 2013; Durukan et al., 2020; Falk et al., 2015; Read et al., 2016). Five studies supported that there were less macrolide resistant mutations with an extended azithromycin treatment than with azithromycin 1gram single dose (Anagrius et al., 2013; Bjornelius et al., 2008; Durukan et al., 2020; Piñeiro et al., 2019; Read et al., 2019).

Two studies that compared the effectiveness of cure rates between azithromycin 1.5 grams versus the higher dose of 2.5 grams of azithromycin, showed that azithromycin 2.5 grams was superior in effectiveness with less development of macrolide resistant mutations (Durukan et al., 2016; Read et al., 2019). The 3 studies that compared single dose 1 gram azithromycin and versus the 1.5 grams azithromycin extended treatment regimen demonstrated that there were no differences in effectiveness (Falk et al., 2015; Manhart et al., 2013; Read et al., 2016). There were four studies that found a decrease in azithromycin effectiveness with continued increased

macrolide resistance (Anagrius et al., 2013; Bissessor et al., 2015; Jernberg et al., 2008; Manhart et al., 2013). In the studies evaluated in this paper, ten of those studies tested and recommend for the use of macrolide resistant mutations to guide the treatment for Mycoplasma genitalium (Anagrius et al., 2013; Bissessor et al., 2015; Couldwell et al., 2013; Chernesky et al., 2017; Dionne-Odom et al., 2018; Durukan et al., 2020; Manhart et al., 2013; Piñeiro et al., 2019; Read et al., 2016; Read et al., 2019). Six of the studies included men that have sex with men, and the findings were consistent in showing that this high-risk population should be considered to have a macrolide resistant mutation Mycoplasma genitalium when diagnosed in either the urethral or rectal area (Couldwell et al., 2013; Dionne-Odom et al., 2018; Durukan et al., 2020; Piñeiro et al., 2019; Read et al., 2016; Read et al., 2019). It was interesting to see that three studies used patient self-collecting specimens for vaginal, first void urine, and rectal swabs (Dionne-Odom et al., 2018; Falk et al., 2015; Lusk et al., 2015). These collection methods were found to be an acceptable alternative for obtaining accurate test results, canceling the need for a practitioner to obtain the specimen (Dionne-Odom et al., 2018; Falk et al., 2015; Lusk et al., 2015). Lastly, four studies indicated that the prevalence of Mycoplasma genitalium is high enough to warrant evaluation in symptomatic patients, with some studies showing prevalence of Mycoplasma genitalium to be the same as, or higher than chlamydia (Chernesky et al., 2017; Dionne-Odom et al., 2018; Lusk et al., 2015; Pond et al., 2014).

There continues to be a knowledge gap with Mycoplasma genitalium, despite its discovery dating back to the 1980's (Taylor-Robinson & Jensen, 2011; Martin, 2021). There is still much more to learn about Mycoplasma genitalium, focusing on whether it is an STI that should be treated asymptomatically requires more in-depth studies (Golden et al., 2017; Martin, 2021). Further research is required on new antibiotics or different treatment regimens because of

the increased resistance developing to current antibiotic treatments (Anagrius et al., 2013; Bissessor et al., 2015; CDC, 2021; Jernberg et al., 2008; Manhart et al., 2013; Martin, 2021). Several studies concluded with similar recommendations for the development of a rapid Mycoplasma genitalium assays to be available to assist clinicians in the diagnoses and treatment of Mycoplasma genitalium (Anagrius et al., 2013; Dionne-Odom et al., 2018; Manhart et al., 2013; Piñeiro et al., 2019).

Clinical Application of Evidence

Inconsistencies on dosage for azithromycin exist in the current recommendations and guidelines (CDC, 2021; Martin, 2021). Two studies found 1.5 grams over five days to be an effective treatment for Mycoplasma genitalium (Anagrius et al., 2013; Read et al., 2016). Yet, five studies showed that the dosage of azithromycin 2.5 grams over 4 days was more effective than the 1.5 grams azithromycin extended treatment (Bjornelius et al., 2008; Durukan et al., 2020; Falk et al., 2015; Jernberg et al., 2008; Read et al., 2019). The CDC recommends two antibiotics for mycoplasma genitalium, the first of which is doxycycline followed by azithromycin or moxifloxacin (CDC, 2021). The use of these 2 antibiotics is known as resistance guided sequential therapy (RSGT) and is also recommended in the British STI guidelines and the Australian STI guidelines (CDC, 2021; ASHM, 2018; Soni, 2019). The use of doxycycline is not to treat for Mycoplasma genitalium, but to decrease the bacterial load (Anagrius et al., 2013; Bjornelius et al., 2008). The effectiveness of this sequential treatment was demonstrated in two Swedish studies that showed doxycycline followed by azithromycin 1.5 grams extended treatment regimen both treated Mycoplasma genitalium and decreased macrolide resistance mutations (Anagrius et al., 2013, Bjornelius et al, 2008). However, these studies were conducted using data that was obtained before 2006 (Anagrius et al., 2013, Bjornelius et al,

2008). The data in these two studies can be considered obsolete, since there are more recent studies have concluded that the current population has an increased macrolide resistance Mycoplasma genitalium, making Mycoplasma genitalium more difficult to treat (Bissessor et al., 2015; Dionne-Odom et al., 2018; Piñeiro et al., 2019; Read et al., 2019). In a meta-analysis review of 21 studies in the efficacy in cure rate of azithromycin for non-gonococcal infection conducted by Lau et al. (2015), it was found that there was a decrease of its effectiveness from 85% in 1999-2008 to 67% in 2009-2013 (Lau, et al, 2015). Furthermore, there have been three studies that found doxycycline to be ineffective in decreasing the bacterial load or decreasing the emergence of macrolide resistant mutations (Durukan et al., 2020; Falk et al., 2015; Read et al., 2019). At this time there doesn't appear to be enough significant evidence on the use of doxycycline prior to azithromycin for treatment of Mycoplasma genitalium, particularly with doxycycline only having a 30% cure rate in current studies (Durukan et al., 2020; Falk et al., 2015; Jensen et al., 2016; Read et al., 2019).

With the increase of antibiotic resistance in Mycoplasma genitalium, a clinician should begin to use tools that are available in evaluating the susceptibility or resistance to an antibiotic that is being prescribed (Anagrius et al., 2013; Dionne-Odom et al., 2018; Manhart et al., 2013; Piñeiro et al., 2019). There is a current laboratory test that is being evaluated by the FDA from SpeeDx that tests for both Mycoplasma genitalium and macrolide resistance concurrently (CDC, 2021; FDA, 2019; SpeeDx, 2020). This laboratory test is commercially available and is currently used in Australia and Europe (ASHM, 2018; Jensen et al., 2021; SpeeDx,2020). The name of the laboratory test is ResistancePlus MG (SpeeDx, 2020). SpeeDx claims to give a rapid result in as little as 3 hours and 10min to both detection of MG and macrolide resistance (SpeeDx, 2020). It is marketed as having a 98% sensitivity for detection of Mycoplasma

genitalium with a 100% specificity (SpeeDx, 2020). Resistance markers are claimed to be at 92.5% sensitivity with 100% specificity for a macrolide resistance-based antibiotic (SpeeDx, 2020). Three studies utilized SpeeDx MG Assay for the detection of Mycoplasma genitalium and macrolide resistant mutations, the ResistancePlus MG Assays demonstrated to be reliable and effective in these studies (Couldwell et al., 2018; Durukan et al., 2020; Read et al., 2019; SpeeDx, 2020).

EBP Recommendation

The evidence-based practice recommendation is taking into consideration the high macrolide resistance mutation that is prevalent at greater than 50% in many countries, including the US (Chernesky et al., 2017; Getman et al., 2016; Moi et al., 2015). There is recommendation against screening and testing for asymptomatic patients for Mycoplasma genitalium at this time due to the insufficient evidence that indicate a benefit outweighs the cost or the harm of increasing macrolide resistance (CDC, 2021; Golden et al., 2017; Jensen et al., 2021; Martin, 2021).

All symptomatic patients coming in with STI symptoms including urethritis, cervicitis/PID should be tested for Chlamydia, Gonorrhea and Mycoplasma genitalium to include the use of resistance detection if available (Chernesky et al., 2017; Dionne-Odom, 2018; Getman et al., 2016; Moi et al., 2015). The specimen order would be a first void urine for males and a self-collecting vaginal swab for females, unless a clinician is performing a pelvic exam, which would allow for a high vaginal swab to be collected at the time of the pelvic assessment (Aptima, 2019).

The choice to treat empirically should be a shared decision between provider and patient, after the patient education on STI's and Mycoplasma genitalium is completed (Elwyn et al.,

2012). Patient education should include but not limited to topics such as emerging antibiotic resistance with the possibility of subsequent STI infections becoming resistant, as well as the possibility of treating with an ineffective antibiotic if empiric therapy is prescribed (Bissessor et al., 2015; Dionne-Odom et al., 2018; Elwyn et al., 2012; Piñeiro et al., 2019; Read et al., 2019).

The recommendation per this EBP guideline is to avoid empiric treatment and give the patient written and verbal education on why it is important to treat per laboratory results (Anagrius et al., 2013; Dionne-Odom et al., 2018; Manhart et al., 2013; Piñeiro et al., 2019). If empiric treatment for a symptomatic patient is required per practitioners' clinical judgment and a clinical shared decision with the patient was made, the prescribing recommended treatment is doxycycline 100 mg by mouth twice a day for seven days with a follow up scheduled in 2-3 weeks or sooner if symptoms persist (CDC, 2021).

If laboratory capabilities are available to evaluate for macrolide resistant mutations it should be conducted (CDC, 2021). If the lab is not available, it should be assumed that Mycoplasma genitalium is macrolide resistant (Chernesky et al., 2017; Getman et al., 2016; Moi et al., 2015). If Mycoplasma genitalium is positive with macrolide resistant mutation detected, treatment with moxifloxacin 400mg by mouth once a day for 7 days (CDC, 2021; Jensen, 2021; Martin, 2021). If Mycoplasma genitalium is negative for macrolide resistant mutation, then treatment is azithromycin 2.5 grams extended treatment over 4 days (Durukan et al., 2016; Read et al., 2019). A test of cure was found to be best performed after a minimum of 3 weeks after initiation of treatment (Falk et al.,2015; Jensen et al.,2021, Martin, 2021).

Summary of Evidence Base Practice Mycoplasma Genitalium Management Recommendation:

- Urine for males/vaginal swabs for females (self-collected or clinician collected)
- If Mycoplasma genitalium is macrolide susceptible (Negative macrolide resistant)

  Azithromycin 2.5 grams over 4 days by mouth:

  On day 1 give 1gram, then on day 2-4 give 500 mg
- If macrolide resistant, test of cure still positive, or symptoms persist then

  Moxifloxacin 400 mg by mouth once a day for 7 days
- If unable to assess for macrolide resistance mutation and positive MG then

  Moxifloxacin 400 mg by mouth once a day for 7 days
- Test of cure with a minimum of 21 days after starting treatment

Patient education on STI is extremely important as to emphasize the need to avoid condomless sexual contact until test of cure is negative to decrease re-infection (Falk et al, 2015; Lusk et al., 2015; Manhart et al., 2013). Notification of all sexual partner(s) in last 60 days, as well as instructing all partners to get evaluated for Mycoplasma genitalium is recommended (CDC, 2021; Golden et al., 2017, Martin, 2021).

Conclusion

Studies for more antibiotic medications are required against Mycoplasma genitalium, attributable to the increasing evidence of macrolide resistance and an emerging quinolone resistance as a cause for concern of M gen becoming a public health threat (Anagrius et al., 2013; Bissessor et al., 2015; Jernberg et al., 2008; Li et al., 2017; Manhart et al., 2013; Read et al., 2019). There should also be an increase in efforts in developing and approving FDA lab test that detect macrolide resistance in Mycoplasma genitalium to have a more directed treatment approach (Anagrius et al., 2013; Dionne-Odom et al., 2018; Manhart et al., 2013; Piñeiro et al.,

2019). Lastly, increase consistency and reliability by the governing bodies for sexually transmitted infections in the United States is required to avoid confusion for clinicians on testing and treating for Mycoplasma genitalium, as well as reduce the time to cure with an effective antibiotic, and improve patient outcomes (CDC, 2021; Martin, 2021; WHO, 2021).

Possible Future Study

Possible study proposal for screening of Mycoplasma genitalium is a prospective evaluation in two different clinics. Testing for Mycoplasma genitalium would be conducted on all patients to include asymptomatic patients in one clinic which would establish prevalence of symptomatic and asymptomatic Mycoplasma genitalium patients. The other clinic would follow the CDC recommendation and test for Mycoplasma genitalium in patients who failed non-gonococcal antibiotic therapy (CDC, 2021). Treatment approaches can also be evaluated in the same cohort. The clinic following CDC recommendations would give the sequential treatment of doxycycline followed by either azithromycin extended treatment or moxifloxacin depending on macrolide resistant sensitivity results. The clinic testing all patients can omit the doxycycline and treat per resistant guided therapy waiting on lab results for macrolide resistant sensitivity before prescribing antibiotic regimen. A test of cure conducted a minimum of 3 weeks after treatment initiation can determine effectiveness of each approach in both clinics. The study can also evaluate if post-treatment macrolide resistance occurred and to what extent in both groups. This will allow to directly evaluate the actual effectiveness that doxycycline has or doesn't have in treating Mycoplasma genitalium and the prevention of macrolide mutation from developing.

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Appendix

Literature Matrix for Journal Articles 1-15

Article Information	Purpose/Aim	Design/Sample	Data Collection/ Instruments Methods/ Procedures	Reliability/Validity	Analysis	Limitations	Results/Finding	Conclusion	Grade
1) Treatment of Mycoplasma genitalium. Observations from a Swedish STD clinic Anagrius et al. (2013)	Objective was to evaluate Doxycycline or azithromycin 1g Vs extended dose azithromycin 1g Observation of macrolide resistance	Cohort Non-experimental Observational Retrospective case study Sample size including loss patients to follow up Men & women 385 Treatment Doxy 216 Azithro 1G 134 Azithro 1.5G 35 Doxy then Azithro 1.5G 72	Patient attending STD clinic in 9 year span 1998- 2005. PCR test for M. genitalium & test of cure. Doxycycline 9 days, azithromycin 1 g single dose and extend azithromycin 500g day 1 then 250g day 2-5 Failure to Macrolide resistance monitored before & after treatment, continued monitoring for macrolide resistance for positive specimens between 2006-2011 6years span	No threats to internal external validity were identified by author No controls of internal or external validity mention-ed PCR was test used with no mention of reliability of PCR for detection of Mgen So internal and external validity threats are of Concern	Fishers exact test	Small sample size well described Limited to Patients in a Swedish STD clinic	Doxycycline 43% effectiveness Azithromycin 1g 91% effectiveness Extended azithromcyin dose 99% effectiveness 6% development of macrolide resistance with use of azithromycin 1g, 7 out of 114 0% macrolide resistance development in extended azithromycin sample	Doxycycline inefficient in treating MG 1 g single dose Azithromycin effective however associated with macrolide resistance and less effective than extended 1.5G macrolide resistance of MG encouraged	G

Overall Synthesis of articles grade: G = Good, F = Fair, P = Poor
Doxy = doxycycline
Azithro = Azithromycin

Article Information	Purpose/Aim	Design/Sample	Data Collection/ Instruments Methods/ Procedures	Reliability/ Validity	Analysis	Limitations	Results/ Finding	Conclusion	Grade
2) Antibiotic treatment of symptomatic Mycoplasma genitalium Infection in Scandinavia: a controlled clinical trial Bjornelius et al. (2008)	Objective was to treatment of tetracycline and azithromycin	Cohort Experimental controlled Open treatment clinical trial Size = 159 Men = 115 Women = 44 Sample was small and women to men ratio was not equivalent	PCR used for MG after NAAT G/C completed Study conducted 1/2004 to 5/2005	Inclusion exclusion criteria clearly identified methods clearly written standardized protocol identified controlled variables in lab results identified	Fishers exact test (2-tailed) Test difference in proportion) Mann-Whitney test Test difference in continuous variables	Significant amount of participant given Doxycline vs Azithro	Ineffective Doxy 17% Vs 1gm azithro 85% Due to ineffective Doxy Treatment they evaluated extended dose 1.5G azithro after doxy failure with 96% effective	Doxy less effective versus azithro Extended course of Azithro 1.5G highly effective after initial treatment with Doxy	G

Overall Synthesis of articles grade: G = Good, F = Fair, P = Poor
Azithro = azithromycin
Doxy = doxycycline

Article Information	Purpose/Aim	Design/Sample	Data Collection/ Instruments Methods/ Procedures	Reliability/Validity	Analysis	Limitations	Results/Finding	Conclusion	Grade
3) High prevalence of multidrug resistant Mycoplasma genitalium and human immuno-deficiency virus infected men who have sex with men in Alabama Dionne-Odom Jodie, et al (2018)	To evaluate MSM HIV prevalence of M.genitalium in the US. Population study completed in Alabama 12/2014 to 11/2016	Cohort It was a Sub-study that was being conducted in an STI HIV primary care clinic in Alabama. Sample = 157	Inclusion and exclusion criteria clearly identified Detection of M. gen via PCR with capability of detecting macrolide resistant mutations clearly presented with detailed information, replication could be carried out	Internal validation was clearly described for the use of PCR probes used. Reliability & validity for instruments used we're analyzed with CLC main workbench 7.8.1	Fisher exact test One-way analysis of variance Kruskal-Wallace test SAS soft-ware	Limited generalizability related to population being very specific Author Identified strength of study being a focused study on rectal infections and filling knowledge gap of fluoroquinolone resistance in US Author identified Limitation of study being sample size	Prevalence In both urogenital & rectal M.gen 17.2% With macrolide resistance in 70.6% to 80% Fluoroquinolone resistant mutation 29.6% Multidrug resistant mutations in 24% chlamydia 16.8% gonorrhea 7%	Most M. gen positive specimen were macrolide resistant in this study Confirms prior studies reviewed by author where they state 51% of M. gen positive adult urogenital infections carry macrolide resistant mutation in the US	G

Overall Synthesis of articles grade: G = Good, F = Fair, P = Poor
MSM = men who have sex with men

Article Information	Purpose/Aim	Design/Sample	Data Collection/ Instruments Methods/ Procedures	Reliability/ Validity	Analysis	Limitations	Results/Finding	Conclusion	Grade
4) Guided antibiotic therapy for M.gen Infection: analysis of mutations associated with resistance to macrolides & fluoroquinolones Piñeiro, Luis et al. (2019)	The aim of this study was to evaluate M. genitalium & its susceptibility to fluoroquinolones or macrolides using rapid molecular technique	Study Based in Spain used rapid probe-based PCR with results in >24 hours, testing for susceptibility to macrolides & conventional PCR assay used to evaluate for fluoroquinolone susceptibility Samples for study between 2014 to 2017 mostly from general population (primary care clinics) 65% of samples, other samples obtained from gynecology-21% emergency room-3%, urology-2%, and STI center-9% Total samples analyze were 8,388 positive M. genitalium detected in 437 of those samples approximate 4%	clearly identified internal controls for reliability and validity mentioned Tables were used and supplemented text well with good information presented	Reliability and validity appeared to be good Confirmation obtained with Retesting of the rapid probe PCR using conventional PCR that took 3 - 4 day	Confidence intervals percentages P values	Population is a Spain-based not United States strength is that most samples came from general population increases generalizability limitation is that there are no FDA approved commercial RT-PCR for M.gen available in US	16.3% Resistance to macrolide detect-ed In range of other studies (35%-72%) Confirmed secondary resistance Related to prior Azithro Use (60%)	Confirmed importance of detection of M. Gen in STI's as well as the effective-ness of using rapid technique to increase guided antibiotic therapy and possibly decreasing macrolide resistant strain mutations in M.gen	G

Overall Synthesis of articles grade: G = Good, F = Fair, P = Poor
Azithro = Azithromycin

Article Information	Purpose/Aim	Design/Sample	Data Collection/ Instruments Methods/ Procedures	Reliability/Validity	Analysis	Limitations	Results/Finding	Conclusion	Grade
5) Macrolide resistance and Azithromycin failure in a Mycoplasma genitalium – infected cohort and response of azithromycin failures to alternative antibiotic regimen's Bissessor et al. (2015)	Aim was to determine 1 g azithromycin efficacy as well as alternative antibiotic regimen such as Moxifloxacin and Pristinamycin (Not available in US)	Prospect of cohort study from July 2012 to June 2013 Sample size was 155 from participants from Australia STI's clinic Total: Males = 112 Females = 43 characteristics Symptomatic males = 107 Symptomatic females = 18	First void urine for males and vaginal samples from females Does not state whether it was self-collected or provider collected Detailed description on procedures for laboratory methods we're discussed	Internal reliability and validity was compromised r/t sample being majority symptomatic male	Fisher exact tests SPSS software version 20 multi variable logistic regression analysis linear regression Determine m gen load differences between pre and post treatment MRM	Mostly male in cohort study mostly symptomatic may not be able to generalized to asymptomatic female They used a self-reported form we're reporting bias can occur	Of 155 participants 56 had MRM Strongly associated with azithro treatment failure 11 only post treatment MRM (not detected in pre-Treatment) Moxifloxacin 88% effective Multi drug resistant patients to azithro and moxifloxacin received Pristinamyosin 100% effective small sample size of 6 participants	Provided more data that the macrolide resistant Mycoplasma is highly prevalent and 1 g azithro becoming less effective. Pristinamycin is a promising antibiotic however it is not available in the United States and more studies are required. Study also established that 14 days is enough time to do a test of cure on mgen	G

Overall Synthesis of articles grade: G = Good, F = Fair, P = Poor
MRM = macrolide resistant mutation
Azithro = Azithromycin

Article Information	Purpose/Aim	Design/Sample	Data Collection/ Instruments Methods/ Procedures	Reliability/ Validity	Analysis	Limitations	Results/Finding	Conclusion	Grade
6) Failure of moxifloxacin Treatment and Mycoplasma genitalium Infections due to macrolide and fluoroquinolone resistance Couldwell et al. (2013)	The purpose of this study was to evaluate whether macrolide resistance was associated with treatment of azithromycin failure	This was a sub study to a prior study done in Australia where patient received azithromycin treatment. They were assessing association between azithromycin failure and macrolide resistance development it was a non-experimental retrospective case study using cohort 2008-2011 from STI clinic based in Australia Sample size for this sub study was 143 specimens tested 53/147 = + MG Sample size = 32 47% were macrolide resistant	Information on data collection, instruments, Methods, & Procedures were explained in detail per article in the original study	Unable to assess data collection instruments Methods Procedures reliability and validity since it was not discussed in this article	NCBI BLAST UGENE1.1 IBM SPSS Bio-Informatics software Fishers exact test IBM SPSS statistics for windows version 2.0	Small sample size not generalizable	47% macrolide resistance related to History of prior 1gm azithro tx 20% related to sexual transmission	Confirmed high prevalence of macrolide resistance Mgen already exist increasing prevalence of fluoroquinolone resistance was noted in the study	G

Overall Synthesis of articles grade: G = Good, F = Fair, P = Poor
Azithro = Azithromycin

Article Information	Purpose/Aim	Design/Sample	Data Collection/ Instruments Methods/ Procedures	Reliability/Validity	Analysis	Limitations	Results/Finding	Conclusion	Grade
7) Mycoplasma genitalium antibiotic resistance - mediating mutations in Canadian women with or without chlamydia Trachomatis infection Chernesky et al (2017)	Objective was to study prevalence in Canada determining (provinces) mycoplasma genitalium is more prevalent and mutations of antibiotic resistance. Also assessing association of MG with positive chlamydia.	non experimental Retrospective cohort Use of remnants of prior vaginal specimens Sample size 985	Data collection was not discussed since they were using prior specimens Data collected at different STI clinics. All specimens were shipped to same laboratory Instruments and Procedures followed were discussed in detail	Reliability & validity Controls were used, matching was done confirmatory testing it was also performed on specimens	Prevalence ratios Chi-square	Good size sample however limited to symptomatic woman as population of study	73.3% positive MG. 47.3% macrolide resistance 1.9% fluoroquinolone resistance	MG strong association with Chlamydia High prevalence of mutations in MG for macrolide resistance	G

Overall Synthesis of articles grade: G = Good, F = Fair, P = Poor

Article Information	Purpose/Aim	Design/Sample	Data Collection/ Instruments Methods/ Procedures	Reliability/Validity	Analysis	Limitations	Results/Finding	Conclusion	Grade
8) Cervicitis aetiology and case definition: a study in Australian women attending sexually transmitted infection clinics Lusk et al. (2015)	Define cervicitis and find associations with cervicitis	Cross-sectional study 558 women participants 3 different STI clinics based in Australia 2006-2010	Well described Clinicians attended standardized training	Good reliability and validity Increased with blinded laboratory scientist to assess for microscopic cervical gram stain and whether it agreed with clinicians	Multi-variant analysis Prevalence ratios Chi-square Long binomial regression	Convenience sample Woman in STI clinic – not generalize since it's very specific and may not Represent whole community Gram stain not a good predictor for MG since it doesn't stain, no cell wall	Positive samples CT = 5.8% MG = 3.8% TV = 3.9% NG = 1.1% Cervicitis = associated strongly with vaginal dis-charge	CT, MG, NG, and TV all associated with cervicitis Best definition is cervical discharge or Combination of cervical discharge & micro	G

Overall Synthesis of articles grade: G = Good, F = Fair, P = Poor
CT = Chlamydia Trachomatis
NG = Neisseria Gonorrhea
MG = Mycoplasma genitalium
TV = Trichomonas Vaginalis

Article Information	Purpose/Aim	Design/Sample	Data Collection/ Instruments Methods/ Procedures	Reliability/Validity	Analysis	Limitations	Results/Finding	Conclusion	Grade
9) Resistance guided antimicrobial therapy using doxycycline, Moxifloxacin, and Doxycycline- 2.5 g Azithromycin for the Treatment of Mycoplasma genitalium infection: efficacy and tolerability Durukan et al (2020)	Microbial cure: Doxy-2.5G Azithro Doxy-Moxifloxacin Tolerability & adherence Development of macrolide resistant mutations following Doxy-2.5G Azithro	Prospective clinical evaluation Cohort April 2017- June 2018 Detailed inclusion & exclusion criteria could be replicated Total sample treated with RGT 588 Other Exclusions = 69 and Loss of follow up = 136 383 actual sample analyzed Female - 81 Male – 106 MSM - 196	Detailed discussion of instruments Methods and Procedures used Resistance Plus MG (SpeeDx) Transcription mediated amplification to diagnose chlamydia (Hologic) and/or gonorrhea Sanger sequencing of 23S rRNA gene to control SpeeDx	Good reliability and validity Retesting and confirmation was completed Standardized templates and procedures used	Univariable Logistic regress-Ion STATA version 12 Prevalence ratios Proportion calculation Confidence intervals	Selection bias Loss of follow up bias Possible Funding bias related to SpeeDx and Hologic	Doxy-moxifloxacin 92% cure With 8% failure Doxy-Azithro 95.4% cure With 4.6% failure 100% post macrolide resistance 5/5 Posttreatment	Study provided evidence that Doxy Followed by Azithro 2.5G in macrolide susceptible or moxifloxacin for macrolide resistant strains are highly effective High level of new post treatment macrolide resistant strains MG were seen in this study	G

Overall Synthesis of articles grade: G = Good, F = Fair, P = Poor
Doxy = Doxycycline
Azithro = Azithromycin
RGT = resistance guided therapy
MSM = men who have sex with men

Article Information	Purpose/Aim	Design/Sample	Data Collection/ Instruments Methods/ Procedures	Reliability/Validity	Analysis	Limitations	Results/Finding	Conclusion	Grade
10) Azithromycin 1.5 g over five days compared to 1 g single dose in urethral Mycoplasma genitalium: impact on treatment outcome and resistance Read et al. (2016)	Evaluate effectiveness Azithro 1.5 g over five days versus Azithro 1 g And Evaluate pre- and post-treatment macrolide resistance mutations on 23 s rRNA gene	Retrospective longitudinal cohort case studies 2012-2013 1g Azithro Extended Azithro Regimen 1.5grams over 5 days 2013-2015 Sample was only symptomatic men with NGU Size = 106 MSM = 41/106	Well described Collection, Instruments, Methods, Procedures, inclusions and exclusions	Internal and external validity and reliability threats r/t collection of samples Good validity and reliability and laboratory methods used	Fisher exact Wilcoxon rank-sum test Binomial exact distribution T-test Odds ratios & confidence intervals Logistic regression model 2 sample Z test	Selection bias Non generalized to community	Azithro 1.5G extended Cure rate 58% Azithro 1G cure rate 52% Prost-treatment MRM Azithro 1.5G 12% Post treatment MRM Azithro 1G 18% Pretreatment: Macrolide resistance = 52%	MSM Significantly associated with treatment failure No significant difference in MRM development between extended Azithro 1.5G vs Azithro single dose 1G	G

Overall Synthesis of articles grade: G = Good, F = Fair, P = Poor
Azithro = Azithromycin
MRM = macro,ide resistance mutations
MSM = men have sexual with men

Article Information	Purpose/Aim	Design/Sample	Data Collection/ Instruments Methods/ Procedures	Reliability/Validity	Analysis	Limitations	Results/Finding	Conclusion	Grade
11) Standard treatment regimens' for nongonococcal urethritis have similar but declining cure rates: a randomized controlled trial Manhart et al. (2013)	Azithro 1g vs Doxycycline 100mg twice a day for y days Treatment for NGU focus on MG	Single center STI clinic, randomized controlled, double blinded, parallel group superiority trial (detect differences in group) in Washington state 2007-2011 Size = 606 304 = active Azithro 302 = active Doxy Loss of follow up = 123 Didn't meet revised inclusion criterion = 61 Total loss of subjects = 184 (30%)	Good data collection, instruments, methods, and procedures used discussed Study could be repeated	PCR used for MG detection via urine	O-Brian Fleming stopping rule Related to low cure rates of M.gen they added 1 year Pearson x-2 test	Randomized Double blinded (participants, clinicians, staff) Protocol was modified a couple of times (Added Moxi if persistent) Considered loss of follow up as clinically cured in analysis Made up for this with a sensitivity analysis Volunteer sample	Azithro 63% Cure rate MG Doxy 48% Cure rate MG Microbiologic cure rate was lower Azithro 40% Doxy 30%	Declining effectiveness of standard NGU treatment of both Azithro and Doxy	G

Overall Synthesis of articles grade: G = Good, F = Fair, P = Poor
Moxi = Moxifloxacin
Azithro = Azithromycin
Doxy = Doxycline

Article Information	Purpose/Aim	Design/Sample	Data Collection/ Instruments Methods/ Procedures	Reliability/Validity	Analysis	Limitations	Results/Finding	Conclusion	Grade
12) Time to eradication of mycoplasma genitalium after antibiotic treatment in men and women Falk et al. (2015)	Evaluate how long it takes for a negative test after starting treatment Also monitor antibiotic resistance development	Cohort Prospective longitudinal observational cohort study randomized into 2 treatment groups. 2010-2014 STI clinic in Sweden Sample size 191	PCR with Sequencing for MG detection & macrolide resistance Controlled lab	Good reliability & validity Since same lab used for all specimens Possible Internal and external threat related to having patients collect own specimens' multiple times	Kaplan-Meier survival plots Log rank Analysis	Selection bias r/t STI clinic Fatigue bias (from participants since they were asked collect samples multiple times - 12 times) Reporting bias Related to unprotected intercourse during study	Neg results with treatments: Moxi: 4/5 (80%) 1g Azithro 9/15 (60%) Azithro 1.5G 47/62 (75%) Doxy 3/8 (37.5%)	Test of cure should be completed at 3 to 4 weeks No significant clearance between 1g versus extended Azithro 1.5 g No significant difference MG bacterial load and developing macrolide resistant mutation or clearing infection	G

Overall Synthesis of articles grade: G = Good, F = Fair, P = Poor
Moxi = moxifloxacin
Azithro = azithromycin
Doxy = doxycycline

Article Information	Purpose/Aim	Design/Sample	Data Collection/ Instruments Methods/ Procedures	Reliability/Validity	Analysis	Limitations	Results/Finding	Conclusion	Grade
13) High prevalence of antibiotic resistant Mycoplasma genitalium in nongonococcal Urethritis: The need for routine testing and the inadequacy of current treatment options Pond et al. (2014)	The aim of this study was to evaluate prevalence of M genitalium in comparison to more well known Urethritis organisms, to include frequency resistance mutations to macrolides & fluoroquinolone	Observational cohort study Sept – Dec 2011 Sample size: 217 110 with urethritis 102/110 with NGU	Well described test could be replicated Data provided	Sample selection bias May Threaten Internal/ external Validity & Reliability	Power 80% Chai-square McNemar test	Small sample size Volunteer sample	All urethritis: Chlamydia 17/109 MG 17/110 Gonorrhea 7/109 Trichomonas 2/110 NGU: MG 17/102 16.7% Chlamydia 15/102 14.7% Trichomonas 2/102 2%	MG is as prevalent as Chlamydia Or possibly even higher Macrolide resistsnt mutations at 40% Above gives a good indication on why MG urethritis/ cervicitis symptomatic patient work up	G

Overall Synthesis of articles grade: G = Good, F = Fair, P = Poor

Article Information	Purpose/Aim	Design/Sample	Data Collection/ Instruments Methods/ Procedures	Reliability/Validity	Analysis	Limitations	Results/Finding	Conclusion	Grade
14) Azithromycin and Moxifloxacin for microbiological cure of Mycoplasma genitalium Infection: an open study Jernberg et al. (2008)	Hypothesis was that azithro had lower cure rate in Norway where 1g azithro was routinely given as a treatment for NGU	Cohort Retrospective Survey open study Between 5/2005-12/2006 Sample size 10,109 Symptomatic Men & women Sample size Pos MG 452	Collection, Procedures, Instruments all discussed in the article In detail Urine samples from both male/female Vaginal swab samples also obtained from females PCR used One central lab used Tx's: 1g azithro Extended azithro 1.5G Ofloxacin 200mg twice a day x 10days Moxifloxacin 400mg x7 days	Good reliability and validity on testing for MG Loss of follow up threatens validity Ranging from 17%-22%	Epi-Info	Strength Sample size 10,109 Survey study	+ MG 452/10,109 4.5% 48/452 Co-infection with chlamydia Effectiveness Azithro 1g 79% Azithro 1.5G Extended 78% Ofloxacin 44%-58% Moxifloxacin 100	Norway whom uses Azithro for NGU Treatment had decreased effectiveness compared to Sweden whom uses Doxy for routine NGU Treatment Azithro In 2008 was an effective treatment at 79%, however Moxi Effective-ness was at 100%	G

Overall Synthesis of articles grade: G = Good, F = Fair, P = Poor
Azithro = Azithromycin
Moxi = Moxifloxacin
Doxy = doxycycline

Article Information	Purpose/Aim	Design/ Sample	Data Collection/ Instruments Methods/ Procedures	Reliability/Validity	Analysis	Limitations	Results/Finding	Conclusion	Grade
15) Outcomes of Resistance guided sequential Treatment of Mycoplasma genitalia infections: a prospective evaluation Read et al. (2019)	Evaluate sequential antibiotic treatment following doxycycline using resistance guided laboratory test result to determine macrolide (Azithro 2.5G) versus fluoroquinolone approach (Sitafloxacin)	Prospect Ive evaluation Sample size 244 Female 52 Male 68 MSM 124 (more than 50%)	Study described Collection, Instruments, Methods, Procedures good. SpeeDx Resistance/ Plus was used and has been consistently validated Study could be be replicated with info provided	Good reliability & validity Instruments and Methods and Procedures used have all been well validate	Univatate Logistic Regression Paired T-test Chi-squared test Exact methods for confidence intervals	External limitation of are patient sexual practices during or after treatment but before test of cure Can all affect outcomes Bias of Loss of of participants since study started with 429 pos MG only 56% were included in this study No control group Funding conflict: SpeeDx provides research funding for STI clinic	Doxy then Azithro 94.8% Doxy then Sitafloxacin 92.2% Macrolide resistance Post treatment 2.6%	Sequential antibiotic therapy had minimal side effects per study. More than 90% effective With use of resistance guided treatment	G

Overall Synthesis of articles grade: G = Good, F = Fair, P = Poor
Azithro = Azithromycin