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Expedited Partner Therapy Using Oral Cefixime and Oral Azithromycin for Gonorrheal and Chlamydial Infections among Adult Outpatients in the United States

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EXPEDITED PARTNER THERAPY USING ORAL CEFIXIME AND ORAL AZITHROMYCIN FOR GONORRHEAL AND CHLAMYDIAL INFECTIONS AMONG ADULT OUTPATIENTS IN THE UNITED STATES

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Abstract

Sexually transmitted infections (STI) such as *Neisseria Gonorrhoeae* and *Chlamydia Trachomatis* pose a challenge to the healthcare system worldwide. Treating sexual partners is as crucial to controlling the spread of these infections as treating index patients. However, because of problems associated with stigma, reaching affected populations, and ensuring follow-up, unique solutions are require to ensure partners receive treatment. One solution is Expedited Partner Therapy (EPT). EPT refers to treating patients, and providing necessary medication for both patient and partner. Current recommendations are for oral doses one gram of azithromycin and 400 milligrams of cefixime. This literature review looked at thirteen studies, and aimed to determine whether EPT is still superior to standard partner notification at reducing further infection, and reinfection in adult Gonorrhea and Chlamydia (GC) patients in the US. Research indicates that EPT remains a viable, cost-effective measure at controlling the spread of GC infections. EPT appears to be the best available option despite use of second-line treatments in resistance-prone infections. Additionally, there is a need for future, large-scale, US-based randomized controlled trials to unequivocally show the continued effectiveness of EPT.

Keywords: Gonorrhea, Chlamydia, EPT, STI, Azithromycin, Cefixime, Gemifloxacin, Expedited Partner Therapy, Sexually Transmitted Disease, Ceftriaxone, Partner Notification, Partner Treatment

Despite continuing public health efforts, sexually transmitted infections (STI) caused by *Neisseria Gonorrhoeae* and *Chlamydia Trachomatis* continue to impose a significant healthcare burden in the United States and beyond. One of the central problems with interventions aimed at controlling the spread of these infections is how to treat a patient's partners and sexual contacts. Traditional methods employed in Emergency Departments, STI/Public Health, and primary care clinics rely on the patient to relay their current infectious state to their partners and contacts. Additionally, the onus is on the patient to encourage the partner or sexual contact to present for treatment.

The current treatment regimen for *N. Gonorrhoeae* infection recommended by the Centers for Disease Control and Prevention (CDC) is 250 milligrams (mg) ceftriaxone given intramuscularly (IM), and azithromycin 1 gram (g) given orally as a single in-clinic treatment. The CDC recommended treatment for lab-confirmed chlamydial infection without gonorrheal co-infection is azithromycin 1g orally as a single, in-clinic dose. These current regimens are first-line treatments in order to avoid rising resistance among both *N. Gonorrhoeae* and *C. Trachomatis* strains in the United States.

Expedited Partner Therapy (EPT) is one method by which clinicians can attempt to treat sexual contacts of infected gonorrheal and chlamydial (GC) patients without the contact needing to present themselves for treatment. In most scenarios, patients are given packets containing cefixime 400 mg oral tablets along with azithromycin 1g oral tablets to give to their partners. The advantages of this treatment method are that it enables contacts who are unwilling or hesitant to present themselves in clinic a way to receive treatment, and it allows patients a more effective method of notifying partners of their infection and providing on the spot treatment.

Statement of the Problem

The crucial drawback of EPT is found in the *choice* of antibiotics. As the recommended first line treatment (ceftriaxone) is given in-clinic as an injection, EPT packets must contain a second-line choice which must be available orally. In the US, that choice is currently cefixime. The purpose of this study is to examine the body of literature surrounding cefixime, gonorrheal and chlamydial (GC) infections, and EPT specifically to see whether the use of a second-line drug treatment is still superior to following more traditional methods of partner notification and clinic presentation.

It is important to note here that any time a treatment modality is used that explicitly avoids evidence-based best practices, we can consider such a modality a form of *harm reduction*. As such the choice may be between an inferior treatment, or no treatment at all. This literature review will attempt to examine relevant studies to determine whether EPT remains the superior choice compared to the potential for no treatment of GC infections in sexual partners. Some studies are large, ecological surveys of GC epidemiology. Some are retrospective cohort studies, and a few are randomized, controlled trials often conducted at the state or local public health jurisdictional level.

This is a unique situation in infectious disease treatment where first-line treatment is not possible due to the route of administration, and the second-line treatment has been shown to be demonstrably inferior. Therefore, researchers and clinicians need to know: should we still be providing cefixime to partners who can't or won't seek treatment on their own? Does the benefit of treating potentially resistant strains of gonorrhea with cefixime outweigh the risks of re-infection or treatment failure?

Research Question

Is Expedited Partner Therapy using oral cefixime and azithromycin for treatment of GC Infections still superior to standard partner notification among adult outpatients in the US in reducing further infection and reinfection rates?

Research Methods

This project was performed as a literature review, primarily aimed at examining randomized, controlled trials, retrospective studies, cohort studies and other observational analyses. The primary databases which were searched were PubMed and Cochrane Database. Primary parameters for the searches included peer-reviewed articles and studies conducted within the last 20 years which discussed or studied the primary themes of this review: Patient-Delivered Partner Therapy (a term often used interchangeably with EPT), use of oral cefixime for GC infections, and the rise of antibiotic resistance in GC infections. Initial parameters were set to include studies published within the last five years, however it was determined that due to the relative paucity of research on EPT, several key studies from the early 2000's should be included. This required us to broaden the search period to the last 20 years of peer-reviewed research.

PubMed was primarily searched using MeSH headings. Seven relevant MeSH headings were identified: "Cefixime", "Ceftriaxone", "Azithromycin", "Gonorrhea", "Chlamydia", "Sexually Transmitted Diseases, Bacterial", and "Contact Tracing." Various MeSH subheadings were then included under each top-level subject heading. Additional general PubMed search terms identified were "Partner Notification", "Expedited Partner Therapy", and "Patient-Delivered Partner Therapy". Cochrane Database was searched using the MeSH

headings as noted above, entered as primary search terms (in addition to the general PubMed terms). A total of thirteen studies were identified using the above search terms, with publication dates ranging from 2005-2018. Seven were randomized, controlled clinical trials, five were retrospective and cohort analyses, and one was a Cochrane Review statistical meta-analysis. This was not a systematic review of EPT and ancillary literature, nor a comprehensive meta-analysis (although one meta-analysis was reviewed), rather an update looking at the most current state of EPT-related literature.

Expedited Partner Therapy vs. Standard Partner Notification

Performing large, randomized controlled trials of interventions such as EPT is difficult at the best of times. As such, the study by Golden, et al. (2015) represents the most comprehensive RCT to date looking at EPT use in the United States. The authors introduced EPT to county-level public health jurisdictions across Washington State in a stepwise manner over the course of 6 months. They used GC infection rates and provider use of EPT as the primary outcomes. The results showed significantly higher uptake of EPT use among providers in the study jurisdictions, however the actual impact on infection rates was less clear after statistical analysis.

The statistical analysis showed significance when measuring the rates of EPT use (as measured by the number of patients receiving EPT to take to their partners) which increased from 18% to 34% across the population, with $p<0.001$ (Golden, et al., 2015). When looking at the second primary outcome, positive gonorrheal test rates and gonorrheal incidence, the confidence intervals for both reductions crossed one, with $p=0.15$ and 0.45 respectively. The authors correctly surmised that there was no statistically convincing evidence that EPT uptake significantly decreased these two metrics.

Additional drawbacks of the study were noted by the authors. Certain communities were excluded from the study (notably Seattle/King County) which already had robust EPT programs and could not be "feasibly stopped and restarted [for the study]." (Golden, et al., 2015). The authors devoted a large portion of their discussion to the potential lack of statistical power (especially the potentially small number of participants for the size of the overlying population). Another drawback noted by this literature review was the primary gonorrheal metrics being measured through GC tests administered to women aged 14-25 presenting to local STI and Planned Parenthood clinics. This conspicuous lack of male metrics may be due to the lack of high-volume clinics catering specifically to men, but nevertheless puts the generalizability of these results into question. This is especially true as the EPT interventions were not limited to female patients.

As noted in the previous study, direct studies examining EPT head-to-head with standard partner notification are relatively few in number. The study by Golden and Kerani, et al. (2005) looked at a much smaller population than its 2015 follow-up. In this particular case, patients presenting with laboratory-confirmed GC infections at one of two Seattle/King County public STI clinics were randomized to one of two interventions: either a cefixime/azithromycin EPT packet to give to their known sexual partners, or referrals for standard partner notification and invites for contacts to present themselves for treatment.

Statistical results showed that EPT was associated with lower persistent or recurrent *gonorrheal* infections than standard partner notification ($p=0.01$). Interestingly, recurrent or persistent *chlamydial* infection rates were not lower among EPT participants with a $p=0.17$. The relative risk associated with EPT was shown to be 0.75, meaning the EPT group had only 75%

chance of experiencing recurrent or persistent infection as compared to the control of standard partner notification. In this last case, results were noted by the authors to be statistically significant with the 95% confidence interval including the noted value and not crossing one (Golden, et al., 2005).

Despite these promising results, there were several drawbacks noted in this study. Perhaps most importantly, this study was conducted in 2005, over 13 years ago. Typically, such long intervals might lead one to preclude such studies on their face, however it was decided that because this particular study was so clearly on point with our research question (and so few studies were found that were) that it warranted inclusion. However, 2005 is not 2018 and antibiotic resistance has changed significantly. In 2005, the CDC still recommended oral cefixime as a first line treatment for gonorrhea. These results should be assessed with this knowledge in mind.

Additionally, as far as the included population, this study notably excluded self-identified men who have sex with men (MSM). The population included self-identified women and heterosexual men, arguably missing a key population for intervention (Golden, et al., 2005). This would therefore possibly impair the generalizability of this study to all adult populations in the US. Additionally, the lack of strong evidence for chlamydial cure following EPT was not thoroughly discussed, although the authors noted it was beyond the scope of this particular study. In summary, this 2005 study might serve as a valuable blueprint for further studies into EPT, especially the randomized controlled trials.

Although referencing older studies (as noted above) is often less than ideal, Kissinger, et al.'s (2005) study represents the second such study evaluated for this literature review. In this

randomized controlled trial, a public STI clinic in New Orleans, Louisiana enrolled male patients presenting with confirmed *C. trachomatis* and *N. gonorrhoeae* infections. This trial was notable for being a targeted, in-depth comparison of EPT at a single source where control of interventions was directly at patient-level. Unlike the previous two EPT randomized, controlled trials, the New Orleans study also tracked patient follow-up by quantifying *how often* the patient's contacts *took the EPT medications*. This is an important metric for any evaluation of EPT results.

Statistical analysis showed several promising results, notably that the study was significant for how often patients completed their randomized intervention. 69% of EPT patients gave the medications directly to their partners versus 49% of the partner referral patients told their contacts to get treated. For this particular result, statistics were encouraging with $p<0.001$. Crucially, the evaluation of follow-up GC infection rates was lower for EPT patients (23% positive for re-infection versus 42.7% for standard partner referral patients), and for this statistic, again $p<0.001$. However, while the statistics were generally presented as favorable in showing the significant impact of EPT against standard of care, no in-depth discussion of the statistical methodology was included, raising concerns about reproducibility (Kissinger, et al., 2005).

Perhaps the most glaring drawback in this study's relevance was its use of ciprofloxacin for a period during 2003 (Kissinger, et al., 2005). Ciprofloxacin is no longer a recommended treatment for GC infections as of 2018, as resistance is widespread. This makes it difficult to generalize the study to today's clinical environment where ciprofloxacin is no longer a viable option. Additionally, the population was relatively small, enrolling only male patients at one STI clinic in one city. Notably (and perhaps unintentionally), over 95% of participants were of

African-American race, which has the potential to skew results and impair generalizability. Nevertheless, this study is important because, like the previous trial reviewed, it provides important blueprints for how to potentially reproduce such trials in the current clinical environment.

Partner Notification Methods - Meta-Analysis

Our literature review revealed one systematic review of randomized, controlled clinical trials directly discussing the effectiveness of EPT (Ferreira, et al., 2013). This Cochrane review included eight trials covering EPT: Cameron et al. (2009), Golden et al. (2005), Kerani et al. (2011), Kissinger et al. (2005), Kissinger et al. (2006), Nuwaha et al. (2001), Schillinger et al. (2002) and Schwebke et al. (2010). The benefit of systematic reviews such as those found in the Cochrane Database lies in the strength of their evidence. Hierarchically they offer the best panoramic view of the strength of clinical evidence for or against a particular intervention. In this case, EPT was shown to be superior to traditional partner referral but *not* superior to "enhanced partner referral" which presumably included more robust interventions aimed at encouraging partners to seek treatment. Ferreira, et al. (2013) noted that any effective EPT program should therefore be sure to include these enhanced measures as the evidence clearly showed that each was preferable to standard partner referral, but that the sum was greater than the two parts.

Statistically, this Cochrane review surveyed the 6 identified EPT-based randomized controlled trials and noted that EPT was again superior to standard partner referral at preventing reinfection (RR of 0.71 with a 95% confidence interval 0.56-0.89, which included the named value and did not cross one) (Ferreira, et al., 2013).

The drawback to this particular systematic review is the same that the previous studies experienced: lack of timely relevance. None of these RCTs directly demonstrate the continued superiority of EPT over standard partner referral in the *current* microbiological environment. Cefixime has since been relegated to second-line therapy, and resistance to first line ceftriaxone injectable therapy in North America is being reported in the literature (Lefebvre, B. et al., 2018 and Papp, J.R., et al., 2018). However, it is important to note that drawbacks can be seen as positives depending on the perspective. In this particular case, EPT continues to be recommended if standard patient referral is impossible or unlikely. Nevertheless, the landscape of antibiotic resistance appears to be continually shifting. Therefore, this Cochrane review highlights the need for additional RCTs to evaluate EPT with current microbiological trends.

Efficacy of Cefixime as Second-Line Treatment

In addition to RCTs evaluating EPT, there are many other studies indirectly related to our research question that may be of benefit. In the case of Whittles, et al.'s (2017) study on cefixime resistance in *N. gonorrhoeae*, we see a statistical argument that cefixime may not be as ineffective as recently thought. This study was essentially a large retrospective cohort study which was then applied to a complicated statistical model. Men who have sex with men (MSM) gonorrheal infection data was gathered from 2008 to 2015 in England through the National Health Service. This timeframe is important because it represents the beginning of the ceftriaxone era in GC treatment.

Statistically, the authors of this study applied two concepts: mathematical modelling and Bayesian inference (Whittles, et al., 2017). They detected a significant decrease in cefixime resistance in England (under 1% as of 2014), however statistical significance of this finding was

neither noted or discussed. Notably, they showed evidence that cefixime resistance has actually diminished among common strains of *N. gonorrhoeae*. They argued the statistical model showed that cefixime could be re-introduced to treat a minority of gonorrhea cases without causing a second resistant epidemic. The central hypothesis of this study is that MSM in England were previously a population heavily infected with the G1407 strain of gonorrhea, which was a prime mediator of cefixime resistance (Whittles, et al., 2017). By introducing first-line ceftriaxone/azithromycin dual therapy, the G1407 strain is declining, causing cefixime resistance to decline with it.

A serious drawback of this study was highlighted in a review article by Unemo and Althaus (2018) in which they argued that cefixime was removed from treatment in favor of ceftriaxone but cefixime resistance remains high. As such, this hypothesis may be less durable outside of the specific English MSM population on which it was based. Because of this, and the prospective and hypothetical outlook of using a mathematical model make this study less reliable in showing the *current* utility of oral cefixime for use in EPT. Drawbacks in patient population and setting (MSM and England, respectively) also limit the generalizability of these findings to the adult population in the United States.

Whereas the previous study attempted to feed gonorrhea treatment data into a mathematical and predictive model, Town, et al. (2018) conducted a retrospective study aimed at evaluating the effectiveness of previously used antibiotics on current strains of *N. gonorrhoeae* in England. They evaluated susceptibility to three drugs: penicillin, ciprofloxacin and cefixime. By using clinical isolates from STI testing across England, they performed susceptibility testing

to see which drugs remained effective. In this case, the 95% susceptibility threshold for acceptable antibiotic use by the World Health Organization was used.

Results showed predictably that only cefixime approached the 95% threshold of susceptibility. Because the samples were primarily stratified by sexual orientation (MSM vs. heterosexual), the authors showed that cefixime was significantly more susceptible among heterosexuals than among MSM (between 96-96% for heterosexuals, $p<0.001$ and 81-82% for MSM, $p =0.05$) (Town, et al., 2018).

It should be noted that this was the first study which directly discussed the significance of the 95% threshold for susceptibility. It detailed how the origins for this threshold were "obscure, and originated at a time when there were more antimicrobials that met this criterion than are currently available." (Town, et al. 2018). This is important to note as it brings up the possibility that we may be entering an era where 95% susceptibility may be unrealistic or even impossible as susceptibilities decline. However, the authors recognize this avenue of research is as yet untouched. This study again suffers from generalizability issues in that it focused exclusively on the differences in three previously used drugs comparing their effectiveness between MSM and heterosexual patients. Nevertheless, it does provide population-level data that cefixime use may still be warranted in situations that demand EPT.

Alternatives to Oral Cefixime

According to the CDC, there are only two recommended treatment regimens for uncomplicated GC infections: ceftriaxone IM with oral azithromycin, and as an alternative, oral cefixime with oral azithromycin (the therapy being evaluated in this review) (CDC, 2016). Additional alternative choices exist (although two are non-FDA approved as of January, 2019),

and should be considered when looking at the efficacy of cefixime/azithromycin as the best choice for EPT. To date, the best available evidence for *oral* alternatives are three antibiotics available in oral form: gemifloxacin, zoliflodacin (ETX0914), and solithromycin (CEM-101). Of these, only gemifloxacin is FDA-approved in the US, with zoliflodacin and solithromycin in Phase II/III clinical trials as of 2019.

One study by Kirkcaldy, et al. (2014) looked at using either gentamicin IM plus oral azithromycin or oral gemifloxacin plus oral azithromycin for treatment of gonorrhea. Because EPT by definition requires *oral* treatment, the gemifloxacin regimen is of interest here. Kirkcaldy's study was a randomized, controlled trial including 200 participants in each arm (gentamicin or gemifloxacin). In the case of the gemifloxacin, 99.5% cure rates were achieved for gonorrheal infection.

Statistically, this study was not a comparative trial. The authors described it as "establish[ing] efficacy data for 2 candidate regimes [gemifloxacin and gentamicin]" (Kirkcaldy, et al., 2014). The research question focused on effective GC cure rates for the two treatments, as such 95% confidence intervals did include the 99.5% cure rate described by the authors.

One notable detail described by the authors of the gemifloxacin/gentamicin study regarded potential adverse effects. Current EPT using Cefixime is associated with relatively low incidence of adverse effects (ex: California's department of public health reported no instances of reported adverse effects over 15 years of EPT use) (2016). However, Kirkcaldy, et al. (2014) did note a 7.7% incidence of adverse effects among gemifloxacin patients, notably manifested as vomiting and GI discomfort. This is important considering that EPT patients are by definition

unmonitored and often anonymous. Additionally, an oral medication that causes vomiting might be associated with lower cure rates due to low absorption.

It should be noted that this trial and other evidence pertaining to alternative oral GC therapies all suffer from low power and small sample sizes. Kirkcaldy, et al. (2014) had 200 participants in each arm of the study. A similar study using the Phase II experimental fluoroketide Zoliflodacin (ETX0914) in 2018 had 141 participants (Taylor, et al., 2018), and a much smaller trial using the Phase III experimental macrolide Solithromycin (CEM-101) in 2013 enrolled only 41 patients. The CDC discusses these alternative therapies but notes that their utility is lower because of the potential for GI side effects in the case of gemifloxacin. The CDC also discusses the two novel antibiotics Zoliflodacin and Solithromycin as being of interest but lacking strong enough evidence and their lack of FDA approval to date. (CDC, 2016).

Social and Economic Aspects of Expedited Partner Therapy

Although RCTs are important in properly gauging evidence for EPT's effectiveness, post hoc analyses of EPT acceptance is also crucial to success. Without high uptake by eligible patients, an intervention such as EPT can quickly cross from acceptable harm reduction to wasteful use of resources, especially if evidence shows better infection control could be achieved using other methods. The only post hoc analysis of US EPT programs found in this literature review was conducted by Vainya, et al. (2014) and evaluated the uptake and acceptance by index patients infected with *Chlamydia trachomatis* in STI clinics in New York City. Presumably, the EPT offered was either oral Azithromycin 1g or a combination of Cefixime 400 mg and Azithromycin 1g (in the case of concomitant gonorrhea infection).

Results showed that when adjusting for patients whose partners had already sought treatment or were present at the time of index patient diagnosis, 69.4% of patients accepted EPT from the provider. Notably, the most predictive values for accepting EPT were overt signs of chlamydial infection in index patients and male healthcare providers offering EPT (Odds Ratio 1.32 and 1.30 respectively, with 95% confidence intervals including the named value and not crossing one) (Vainya et al., 2014).

Although this study was retrospective in nature, and excluded MSM, it nevertheless has high utility for the general study of EPT. It should be noted that any robust public health measure (such as EPT) which costs time and money to implement, promote and maintain, can be shown to have poor uptake by the targeted population despite the best of intentions. In the case of EPT, where a second-line antibiotic is being offered in lieu of evidence-based first-line therapy, if uptake is low then serious consideration should be given to whether EPT resources would be better invested in other population-level initiatives. In the case of this study however, it shows that 7 out of 10 eligible patients accepted EPT therapy. (Vainya, et al., 2014). It should be noted however, that this study only looked at chlamydial infections, and while some patients undoubtedly were experiencing gonorrheal coinfection, the generalizability of such results may be of less utility with EPT looking at both gonorrheal and chlamydial infections.

At least one recent study has evaluated pregnant female patients and their acceptance of EPT. Unger, et al.'s (2015) study evaluated EPT within the context of a larger HIV diagnosis program at a women's clinic in Kenya. Women being screened for STIs who had a bacterial infection were then offered EPT in lieu of standard partner referral. This study was notable as the

only study found in this literature review that included *Trichomonas vaginalis* infections by including oral metronidazole in EPT packets if patients tested positive.

Statistically, this study had one notable measure that seems germane to the current research question. In this case, patients were specifically interviewed pre- and post-EPT as to whether fears of partner anger or abuse factored into whether the partner was ultimately treated or not. In this small population, no statistical difference was noted between partners treated and those not as to whether such fears impacted the index patient's willingness to deliver EPT ($p>0.05$ in all cases) (Unger, et al., 2015).

This element is important because not only is this study helpful in evaluating a patient population notably absent in previous studies (pregnant females) but also in evaluating concerns over intimate partner violence. In other words, because any intervention aimed at controlling GC infection should not cause any harm, such results are promising. It should be noted that the authors did not delve deeper into this area of study, and such results should not be viewed as strong evidence for ruling out intimate violence concerns with EPT (Unger, et al., 2015). One of the study's main drawbacks is indeed the small sample size and the prospective nature of the data (prospective cohort study). It nevertheless is helpful and encourages further study of this important social impact of EPT.

Assessing an intervention's cost is an often-overlooked aspect of that intervention's long-term viability and success. In perhaps the most interesting study evaluated in this literature review, Gift, et al. (2011) looked at comparing the cost and cost-effectiveness of EPT versus standard patient referral, using data from two previous studies already examined in this review (Golden, et al., 2005 and Kissinger, et al., 2005). By evaluating the system cost *and* the

individual cost through direct dollar amounts and quality-adjusted life years (QALYs), this study was able to show EPT to be associated with significant cost savings from a systems perspective, however the cost to the individual may be higher based on the number of partners.

Statistically, the main drawback in reviewing this study was the lack of identifiable significance markers. P-values or confidence intervals did not appear within the text or tables, and percentages and numbers did not specify which tests were used to establish significance. The authors describe using the monte carlo method to evaluate numerical results, and this reviewer's rudimentary understanding of the applications of the monte carlo method was not enough to truly evaluate the strength of the evidence (as such its significance may be clear, but beyond our understanding) (Gift, et al., 2011). Nevertheless, the numbers and results presented, if significant, represent good news for EPT. By demonstrating cost savings, larger health systems with commercial payers who may not be using EPT (unlike the often-studied public STI clinics) may be willing to consider the practice.

Unfortunately, the data used from Kissinger et al. (2005) and Golden, et al. (2005) may not be recent enough to demonstrate generalizability to today's healthcare market. The major changes brought forth from the 2012 implementation of the Affordable Care Act (ACA) may have altered the landscape enough to make this data totally irrelevant. It should still be seen as a valuable addition to this literature review given its blueprint for a direct assessment of EPT's cost effectiveness.

At least one study thoroughly discussed a potential disadvantage of EPT. Because EPT is provided as a sort of "end-point" in GC treatment (in other words, partners receive the EPT medication and the "cascade" ends there). Clark, et al.'s (2017) study of partner notification in

EPT therapy among MSM in Lima, Peru discusses what many consider a major shortcoming: the potential to lose partners to valuable follow up care. The question is posed: if partners receive EPT, are they then less likely to present for follow-up testing of HIV and Syphilis? This is an especially pressing question given that STIs such as gonorrhea and chlamydia are known to increase the risk of HIV transmission (Ward & Roenn, 2010).

The results of the study showed that significantly more EPT patients informed their partners of their infection status than those advised through standard partner referral. 83% of EPT patients informed their partners versus 58.3% for standard patient referral (95% confidence intervals for both values included the named value and did not cross one, rendering them statistically significant) (Clark, et al., 2017).

While the results of the study did show statistical significance for a key metric in EPT (successful partner notification), the discussion of the potential for missed HIV/other STI diagnoses and treatment was particularly poignant. This study called for future research into this potential connection. The possibility of *successful* intervention for HIV was actually highlighted as part of EPT, whereby EPT could be targeted to increase partner presentation for follow-up (increased likelihood for follow up). This article correctly discussed how EPT may hold promise for more than just the "short term bacterial STI cure…[but also] the indirect outcomes like HIV and Syphilis." (Clark, et al. 2017).

Results

Of the four RCTs reviewed which looked at EPT as an intervention, one large population-based study showed no significant reduction in reinfection and further infection rates among EPT patients (Golden, et al. 2015), one showed significant reduction (Kissinger, et al.,

2005) and one showed a reduction in gonorrheal infection but not chlamydial infection (Golden, et al., 2005). Additionally, the Cochrane meta-analysis performed by Ferreira, et al. (2013) showed significant reduction in GC reinfection rates compared to standard partner notification, however this meta-analysis used additional studies excluded from this literature review due to age (prior to 2005) or were looking at trichomoniasis infections outside the purview of this review.

Discussion

Although EPT does not employ first-line treatment, the body of current research includes several RCTs which show decreases in recurrence and increased treatment uptake among partners of GC cases. One large RCT did show statistical insignificance when looking at GC re-infection rates (Golden, et al., 2015). However, such studies suffer from either decreased relevance due to age (studies performed over a decade ago), lack of generalizability (focusing on male only, or small men-who-have-sex-with-men populations), or statistical insignificance or low power.

It appears that discussions of whether EPT remains the best practice for partner treatment in GC infections centers on whether it has value as a *harm reduction* intervention. In other words, second-line treatments such as oral cefixime are demonstrably inferior in treating GC infection (Barbee, et al., 2018; Eyre, et al., 2017; Centers for Disease Control and Prevention, 2016; Kirkcaldy, et al., 2016). But should they be used when the alternative is potentially failing to treat infected partners who cannot or will not present to providers? Are other methods such as enhanced partner notification methods more effective than EPT? This literature review shows that in the context of today's antibiotic landscape, the answer is unclear. There have been no

RCTs within the past five years that show EPT to be effective when using oral cefixime, especially when there are now reports of rising ceftriaxone-resistant GC strains (Suay-Garcia and Perez-Gracia, 2017).

Ancillary examination of EPT shows that there is only one readily available oral alternative to Cefixime with comparable cure rates, the late-generation fluoroquinolone Gemifloxacin. However, the most comprehensive evidence to date suggests that despite a high cure rate (99.5%), adverse GI effects render it less desirable than Cefixime, especially with EPT patients (Kirkcaldy, 2014). Such evidence further strengthens the argument that Cefixime-based EPT remains the *best available* option to treat GC infections when partners are not available for in-person treatment.

It should also be noted that this literature review brought up several interesting avenues for potential further research. Evaluating the impact of intimate partner/domestic violence on programs like EPT was discussed in one study and may be an important area in which EPT's lack of furthering harms could be shown (Unger, et al., 2015). Additionally, cost should be viewed as an important metric for EPT's viability. If EPT costs more than it benefits patients and populations, then money might be better invested in other programs. One study (Gift, et al., 2017) did show that this did not appear to be the case, and this strengthens the case for EPT.

Although these studies do seem to show EPT's continued value for STI control, further research is needed to address the shortcomings in the literature and to re-evaluate EPT in the current circa-2018 antibiotic landscape. EPT is a form of harm reduction, and is a known use of second-line treatment when no alternative appears better. Despite this, it nevertheless requires the medical community to ensure it continues to be an evidence-based, recommended best

practice. In the absence of viable alternatives, evidence showing EPT causes further harm, or costs wildly outweighing potential benefits, EPT would appear to be the best available practice for situations in which treating partners face-to-face is impossible or impractical.

Clinical Application

This review has relevance for clinicians practicing in many fields of medicine including family practice, urgent care, emergency medicine, sexual health and STI clinics and public health practice. Because EPT expressly directs providers to prescribe a treatment known to be inferior (cefixime) to the first line treatment, evidence-based best practices are even more important. Should the microbiological climate change to such an extent that cefixime were rendered unusable against gonorrheal infections, EPT would clearly become impossible to justify. Because that does not appear to be the case as of early 2019 in the United States, continued research is justified and necessary to show that the cost, legislation, public health measures and awareness campaigns surrounding EPT are still worthwhile.

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