Chlamydia Treatment Practices and Time to Treatment in Massachusetts: Directly Observed Therapy Versus Pharmacy Prescriptions

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Abstract

Background: Directly observed therapy (DOT) is recommended for the treatment of chlamydia, however pharmacy prescriptions are frequently used. Adherence to DOT and the association between treatment method and time to treatment is unknown. Methods: We conducted a retrospective review of a randomized 2% of laboratory-confirmed chlamydia infections reported to the Massachusetts Department of Public Health from January 1, 2019 to May 31, 2019. Clinicians and pharmacies were contacted to ascertain treatment methods and timing. We assessed frequency of DOT and pharmacy prescriptions in the treatment of chlamydia infection in Massachusetts. We used log rank test to compare time to treatment initiation for patients receiving DOT versus pharmacy prescriptions. Data were stratified according to whether treatment was empiric or laboratory-driven. Key results: We ascertained full outcomes for 199 patients. Eighty patients received DOT and 119 patients received pharmacy prescriptions. DOT was more common among those receiving empiric treatment and pharmacy prescriptions were more common among those receiving laboratory-driven treatment. The median time to treatment was 1.5 days for patients treated with DOT and 3 days for those treated with pharmacy prescriptions. For both groups, the median time to treatment for empiric therapy was 0 days and for laboratory-driven therapy was 4 days. The differences in time to treatment were not statistically significant. Conclusions: Pharmacy prescriptions are frequently used for the treatment of chlamydia in Massachusetts. We did not observe a significant difference in the time to treatment between DOT and pharmacy prescriptions.

Keywords

primary care, pharmacy, disease management, sexually transmitted infections, directly observed therapy

Introduction

Directly observed therapy (DOT) is a cornerstone of the public health management of many infectious diseases. Within the realm of sexually transmitted infections (STIs), DOT has a long established role in the treatment of syphilis and gonorrhea and for which recommended regimens currently require administration of parenteral antibiotics.1,2 DOT became feasible for treatment of chlamydia infection in 1993 when single-dose oral azithromycin was added to Center for Disease Control and Prevention (CDC) STD treatment guidelines.3 In subsequent treatment guidelines, a preference for DOT therapy for azithromycin or the first dose of doxycycline was expressed.4 DOT is often recommended to improve treatment adherence,5,6 however the

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impact of this strategy on time to treatment is unknown. Delayed treatment would be of concern given its association with complications including infertility and increased opportunity for onward transmission of infection.7

By the mid and late 1990s, analyses from Alabama and Maryland found significant delays in patients returning to clinic for directly observed chlamydia treatment with median time to treatment of 12 to 14 days.8,9 More recently, a Massachusetts analysis showed a shorter time to treatment of chlamydia with a median treatment time of 3 days from diagnosis, but did not differentiate between treatment methods used such as DOT versus pharmacy prescription.10 Novel strategies have been employed to improve the effectiveness of DOT for the treatment of chlamydia including use in schools, criminal justice centers, and field-delivered therapy.11-13 However, outside of these niche settings, many clinicians rely on sending prescriptions to patient pharmacies where medications can be filled and taken without direct observation. A cross-sectional review of Title X-funded health centers in California found that a third of new chlamydia cases are treated with off-site prescriptions rather than DOT.14 Associations between treatment method and rates of treatment and time to treatment initiation is unknown.

We sought to understand current treatment practices used in the state of Massachusetts and to assess if treatment method, DOT versus pharmacy prescriptions, was associated with differences in time to treatment.

Methods

We conducted a retrospective review of a random subset of patients with laboratory-confirmed chlamydia cases reported to the Massachusetts Department of Public Health (MDPH) from January 1, 2019 to May 31, 2019. Data were extracted from an electronic surveillance and case management system, the Massachusetts Virtual Epidemiologic Network (MAVEN). This system has been previously described in detail elsewhere.15 Over 90% of cases are reported directly to MAVEN from laboratories, with reported information including the ordering clinician’s name and care location, laboratory test and result date, and patient name, date of birth, gender, and residential address. Currently, 2% of reported laboratory-confirmed chlamydia cases are randomized by MDPH for more in-depth review. For these cases, clinical providers receive a TeleForm that collects standard surveillance variables including patient gender identity, race/ethnicity, and treatment provided. These randomized cases served as the sample for this analysis.

Additional provider follow-up was performed to verify and complete TeleForm data and to ascertain treatment type (ie, DOT or pharmacy prescription). For patients treated with pharmacy prescriptions, we recorded the dates that prescriptions were sent, then contacted pharmacies to determine the dates that prescriptions were picked up. We further classified treatment as empiric versus laboratory-driven. Treatment was considered empiric if patients were provided DOT or had prescriptions sent to pharmacies on the date of visit (prior to availability of laboratory results). All other cases were considered laboratory-driven. Patients with no treatment information or alternative treatment method or location (eg, expedited partner therapy or inpatient therapy) were excluded from the analysis.

Census tract based on patient residential address was used to classify patient residence as urban or rural. Census tract was also used to classify patient residence according to the CDC’s Social Vulnerability Index (SVI).16 This index uses 15 socioeconomic and demographic variables from the US census to characterize community resilience or the ability to withstand external hazards. Census tracts are assigned a percentile rank and categorized as low, moderately low, moderately high, and high, with higher scores representing greater community vulnerability.17,18 Locations of clinical care were categorized as primary care, emergency medicine and urgent care, obstetrics and gynecology, sexual health clinics, and school clinics.

Our outcome of interest was time to treatment, measured as the number of days between date of specimen collection and date of treatment. For patients who received DOT, date of treatment was defined as the date treatment was recorded in the electronic medical record. For patients treated with pharmacy prescriptions, the date of treatment was defined as the date the prescription was picked up from the pharmacy. Patients who were untreated were censored at 60 days.

We compared demographics for patients treated with DOT versus prescriptions using Wilcoxon rank sum and chi-square tests where appropriate. Time to treatment for DOT versus pharmacy prescriptions was compared using a log rank test. This comparison was conducted both for the full cohort and as a stratified analysis by empiric versus laboratory-driven cases. All analyses were conducted using SAS 9.3 (SAS Institute, Inc., Cary, NC). This analysis was exempt from institutional review board review as all data were obtained through public health disease surveillance.

Results

Among the 12 937 cases of laboratory-confirmed chlamydia reported to MDPH between January 1, 2019 and May 31, 2019, 262 were randomized for full case review. Clinics and pharmacies (where applicable) were successfully contacted for 237 patients, and among these 199 were included in this analysis, with 80 in the DOT treatment group and 119 in the prescription treatment group. A total of 8 patients were untreated, 6 of whom were unable to be contacted with test results or declined treatment when contacted. These 6 patients were not included in analysis as they could not be
assigned to a treatment group. Treatment was attempted but not completed in 2; 1 did not return to clinic for DOT and 1 did not pick up their prescription. Details regarding patient flow and reasons for exclusion are shown in Figure 1.

Patient demographics and clinical settings are reported in Table 1. The median age of patients was 23 years and did not vary by treatment group. Females comprised 60% of cases overall and were a significantly larger proportion of those receiving prescriptions (67%) compared to DOT (49%). Patients came from diverse racial and ethnic backgrounds, with 36% non-Hispanic White, 21% Hispanic/Latinx, and 15% non-Hispanic Black. The vast majority (95%) of patients resided in urban locations. The most frequent location of care was primary care, followed by emergency medicine and urgent care, obstetrics and gynecology clinics, and sexual health clinics. There were significant differences in treatment method based upon location of care, with primary care and obstetrics and gynecology providers being more likely to use prescriptions while emergency medicine and urgent care clinics, and sexual health clinics, were more likely to use DOT.

Treatment characteristics are summarized in Table 2. The majority (91.0%) were treated with azithromycin. Approximately one-quarter (26.6%) of patients were treated empirically, while three-quarters (73.4%) received laboratory-directed treatment. A significantly larger proportion of patients receiving DOT were treated empirically compared to those who were provided with pharmacy prescriptions (46.3% and 13.5%, respectively, \( P \)-value <.001).

The median time to treatment was 2 days. The median time to treatment was shorter for DOT (1.5 days) compared to prescription therapy (3 days) although this did not reach statistical significance by log rank test. The maximum time to treatment in the DOT group was 24 days and a maximum time to treatment in the prescription group was 54 days (Figure 2). These outliers were characterized by difficulty contacting patients. When stratified by empiric versus laboratory-directed therapy, the difference in median time to treatment was even smaller. For those receiving empiric therapy there was a median treatment time of 0 days for both treatment groups. The median time to treatment was longer at 4 days for those receiving laboratory-directed therapy regardless of treatment group (Table 3). The difference in time to treatment between empiric and laboratory-directed therapy was statistically significant (\( P \)<.001). Regardless of the treatment approach, the majority of participants were treated within 5 days (85.0% among DOT, 75.6% among pharmacy prescriptions).

Discussion

Our analysis of chlamydia treatment practices in Massachusetts found that the use of pharmacy prescriptions is common, in particular for cases where the decision to treat is based upon laboratory findings. Although DOT is currently recommended by the CDC for the treatment of chlamydia, we observed that it was employed in fewer than half of cases. Our data are reassuring, however, that there is minimal compromise in time to treatment based upon treatment approach. Among the patients for whom we had complete follow-up information, treatment rates were high with fewer than 4% of patients not initiating treatment (8/205). Among those who were treated, the majority received treatment within 5 days. The use of DOT versus pharmacy
prescriptions did not result in a significant difference in time to treatment, and when controlling for the higher proportion of empiric therapy among patients receiving DOT, differences in time to treatment diminished further.

We found differences in how chlamydia treatment is provided based upon patient demographics and provider type. Women were more likely to be treated with prescriptions while men were more likely to receive DOT. This could be due to broader recommendations for asymptomatic screening in women resulting in more laboratory-directed therapy rather than empiric therapy.19 Other demographic factors (age, race/ethnicity, rurality, and social vulnerability) were not significantly different between the 2 treatment groups.

At the provider level, those in primary care and obstetrics and gynecology were more likely to utilize pharmacy prescriptions compared to providers in emergency and urgent care settings, sexual health clinics, and school clinics. This could again be related to differences in presentation and reason for testing, with more asymptomatic screening occurring in primary care and obstetric or gynecologic settings. It is also possible that these settings have less infrastructure to store and administer medications making DOT a less feasible treatment approach.

Our findings are particularly noteworthy at this time when the treatment of chlamydia is shifting toward doxycycline.20,21 There is increasing evidence that 1 week of

Table 1. Baseline Patient Characteristics.

|                        | Total (n = 199) | DOT (n = 80) | Prescription (n = 119) | P-value |
|------------------------|----------------|-------------|------------------------|---------|
| Age, years Med (IQR) | 23.2 (19.9-29.0) | 23.6 (19.9-29.3) | 23.5 (20.3-29.7) | .76     |
| Gender, n (%)          |                |             |                        | .009    |
| Male                   | 80 (40.2)      | 41 (51.3)   | 39 (32.8)              |         |
| Female                 | 119 (59.8)     | 39 (48.8)   | 80 (67.2)              |         |
| Race/ethnicity, n (%)  |                |             |                        | .33     |
| Non-Hispanic White     | 71 (35.7)      | 23 (28.8)   | 48 (40.3)              |         |
| Non-Hispanic Black     | 29 (14.6)      | 15 (18.8)   | 14 (11.8)              |         |
| Hispanic/Latinx        | 42 (21.1)      | 15 (18.8)   | 27 (22.7)              |         |
| Non-Hispanic Asian     | 12 (6.0)       | 5 (6.3)     | 7 (5.9)                |         |
| Other                  | 14 (7.0)       | 8 (10.0)    | 6 (5.0)                |         |
| Missing/unknown        | 31 (15.6)      | 14 (17.5)   | 17 (14.3)              |         |
| Residence, n (%)       |                |             |                        | .50     |
| Urban                  | 189 (95.0)     | 77 (96.3)   | 112 (94.1)             |         |
| Rural                  | 10 (5.0)       | 3 (3.8)     | 7 (5.9)                |         |
| Social vulnerability index, n (%) | | | | .54 |
| Low                    | 47 (24.4)      | 21 (26.9)   | 26 (22.6)              |         |
| Moderately low         | 42 (21.8)      | 19 (24.4)   | 23 (20.0)              |         |
| Moderately high        | 47 (24.4)      | 15 (19.2)   | 32 (27.8)              |         |
| High                   | 57 (29.5)      | 23 (29.5)   | 34 (29.6)              |         |
| Location of care, n (%)|                |             |                        | .001    |
| Primary care           | 82 (42.1)      | 25 (32.5)   | 57 (48.3)              |         |
| ED and urgent care     | 46 (23.6)      | 23 (29.9)   | 23 (19.5)              |         |
| Obstetrics and gynecology | 28 (14.4) | 5 (6.5)     | 23 (19.5)              |         |
| Sexual health clinic    | 25 (12.8)      | 15 (19.5)   | 10 (8.5)               |         |
| Other                  | 14 (7.0)       | 9 (11.3)    | 5 (4.2)                |         |

Table 2. Treatment Characteristics.

|                        | Total (n = 199) | DOT (n = 80) | Prescription (n = 119) | P-value |
|------------------------|----------------|-------------|------------------------|---------|
| Medication, n (%)      |                |             |                        | .13     |
| Doxycycline            | 18 (9.1)       | 4 (5.0)     | 14 (11.8)              |         |
| Azithromycin           | 181 (91.0)     | 76 (95.0)   | 105 (88.2)             |         |
| Treatment type, n (%)  |                |             |                        | <.001   |
| Empiric                | 53 (26.6)      | 37 (46.3)   | 16 (13.5)              |         |
| Laboratory-driven      | 146 (73.4)     | 43 (53.8)   | 103 (86.6)             |         |
doxycycline has higher efficacy compared to single-dose azithromycin for the treatment of chlamydia, in particular for rectal chlamydia in men and women.22-24 Concerns about medication adherence previously dampened enthusiasm for doxycycline as the benefits of confirming treatment completion with DOT are lost when a 7-day course of doxycycline is chosen over a single-dose of azithromycin.25,26 However, a study assessing rates of chlamydia PCR clearance following doxycycline therapy found high success rates in patients with suboptimal adherence (10-14 doses completed in 8 days).6 Furthermore, real-world effectiveness may be greater with doxycycline because of its superior efficacy compared to single-dose azithromycin in the treatment of rectal chlamydia.24 Our analysis adds to this debate by demonstrating that the time to treatment initiation may not be significantly impacted with a shift away from DOT.

Our analysis has additional implications as medical care, including sexual health care, increasingly incorporates telemedicine. The COVID-19 pandemic resulted in calls to reduce in-person medical care including the provision of syndromic management and the preferential use of oral medications provided via pharmacy prescriptions rather than DOT.27,28 While the expectation is that sexual health care will return to prior standard of care, in particular for the treatment of syphilis and gonorrhea, this analysis suggests that the use of pharmacy prescriptions rather than DOT for the treatment of chlamydia may have been safe during the COVID pandemic and may continue to be employed even when social distancing restrictions are lifted.

There are several limitations that should be highlighted. This is an observational analysis describing current chlamydia treatment practices in a single state with a well-insured population, making results difficult to generalize to other states or care settings. There is also the possibility that our findings over-estimate of treatment outcomes because we did not interview cases directly and assumed that the date of medication pick-up was a reasonable approximation for the date of treatment initiation. Furthermore, we were unable to collect treatment information on 45 patients (17.1%). Clinics that were difficult to contact or who had incomplete treatment records may be more likely to have patients who remained untreated. This analysis is restricted to laboratory-confirmed chlamydia cases. Thus, patients treated empirically based upon symptoms or exposure without testing would not be included in this analysis. Finally, our findings were restricted to the 2% of laboratory-confirmed cases randomized for active data collection in the first 5 months of 2019, which may have imperfectly represented all reported chlamydia cases, and made it difficult to draw firm conclusions about treatment practices in smaller

**Figure 2.** Kaplan-Meier curve and log rank test P value for proportion of patients treated by DOT versus pharmacy prescription.

**Table 3.** Time to Treatment by Method and Treatment Type.

| Days to treatment, median (IQR) | Total (n = 199) | DOT (n = 80) | Prescription (n = 119) | P-value |
|---------------------------------|----------------|-------------|------------------------|---------|
| Overall                         | 2.0 (0-5)      | 1.5 (0-5)   | 3.0 (1-5)              | .08     |
| Empiric                         | 0.0 (0-0)      | 0.0 (0-0)   | 0.0 (0-0)              | .13     |
| Laboratory-driven               | 4.0 (2-6)      | 4.0 (2-7)   | 4.0 (2-6)              | .29     |
gender and racial/ethnic populations or the small rural population.

Nevertheless, our analysis of chlamydia treatment practices in the state of Massachusetts found inconsistent use of DOT with more than half of treatment provided through pharmacy prescriptions. Despite this use of pharmacy prescriptions, treatment completion rates were high. Time to treatment was comparable for DOT compared to pharmacy prescriptions, with a trend toward shorter treatment times with DOT likely explained by the preferential use of DOT for empiric therapy. As chlamydia treatment shifts toward doxycycline and as sexual health care services increasingly embrace telemedicine, it is likely that rates of pharmacy prescriptions will increase. This analysis is reassuring that the use of pharmacy prescriptions does not significantly compromise care and may offer practical benefits for patients and providers.

Declaration of Conflicting Interests
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