Exploring Factors Influencing the Efficacy of Dual Therapy in Gonorrhea Treatment: A Retrospective Study

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ABSTRACT

Background: Gonorrhea infection (GO) has a high prevalence in Indonesia, making it a significant public health concern. Effective treatment is crucial in controlling GO. However, the development of resistance has limited treatment options. Current guidelines recommend dual therapy as a syndromic approach. Treatment failures often result from a reinfection due to the barriers to therapy with sexual partners or engaging in sexual activity with newly infected partners. To prevent resistance and control its spread, transmission needs to be minimized. Various factors are associated with recovery as part of a comprehensive resistance control strategy, including appropriate medication, therapy adherence, sexual abstinence during treatment, and regular monitoring.

Methods: This study utilized a retrospective cross-sectional design, analyzing medical records of Gonorrhea patients from the Sexually Transmitted Infections (STI) Outpatient Clinic, Dermatology, and Venereology Department, Dr. Soetomo Public Academic Teaching Hospital, Surabaya, between 2017 and 2021.

Results: Out of 109 GO patients, 64 met the inclusion criteria. The analysis revealed a significant association between dual therapy cure for Gonorrhea and sexual abstinence (p-value = 0.001 < 0.05). Patients who practiced sexual abstinence during therapy were 26 times more likely to achieve recovery compared to those who did not practice abstinence (95% CI = 3.9-170).

Conclusion: Sexual abstinence during therapy emerged as a significant factor associated with cures in GO patients. Emphasizing education on sexual abstinence during therapy is crucial to avoid the "ping-pong" phenomenon of reinfection.
Introduction

Gonorrhea (GO) is a sexually transmitted infection (STI) caused by Neisseria gonorrhoeae. It is primarily transmitted through sexual intercourse, including vaginal, anal, and oral routes, and can also be vertically transmitted from mother to child during childbirth. The global incidence of Gonorrhea is alarmingly high, with an estimated 82.4 million new cases among adolescents and adults aged 15-49 years old in 2020, according to the World Health Organization (WHO) [1].

The rapid increase in resistance of N. gonorrhoeae to antibiotics, including the emergence of fluoroquinolone resistance in the United States, has led the Centers for Disease Control and Prevention (CDC) to no longer recommend the use of fluoroquinolones and to consider abandoning cephalosporins as the sole class of antimicrobials available for Gonorrhea treatment [2]. Furthermore, there has been a reported decrease in sensitivity to cefixime, as indicated by an increase in minimum inhibitory concentration (MIC) in several cases of Gonorrhea reported in Europe since 2010 [3-5].

To enhance the treatment efficacy and minimize the expansion and spread of resistance to cephalosporins, combination therapy utilizing two antimicrobials with different mechanisms of action has been recommended [6, 7]. The Gonococcal Isolate Surveillance Project (GISP) report from 2018 shows that ceftriaxone MIC levels remained low at 0.2%, indicating that it remains an effective treatment option for Gonorrhea [8].

Gonorrhea, although rarely causing direct mortality, leads to significant morbidity and suffering. However, estimates of the benefits of effective treatment have been collected. Despite the high global incidence and prevalence of Gonorrhea, its complications, and the decreasing efficacy of treatment, efforts aimed at eradicating the disease have been minimal. The general requirements for controlling antimicrobial resistance in gonococci are well established and closely tied to disease control itself. Gonorrhea prevention presents complex challenges, particularly in the realm of sexually transmitted infections, where effecting behavioral change is crucial for achieving improved outcomes [9].

To minimize transmission and prevent the development of gonorrhoeae resistance, a comprehensive approach is necessary. This approach involves addressing several factors associated with cure as a strategy to control the spread of resistance. It encompasses reducing the Gonorrhea incidence through appropriate medication, therapy adherence, sexual abstinence during treatment, and routine monitoring.

These factors are influenced by the interplay of epidemiological elements, including the host, the agent (N. gonorrhoeae), and the related environment. A study conducted by Purnamasari, entitled: "A Retrospective Study: Characteristics and Management of Gonorrhea," emphasizes t
variable characteristics of Gonorrhea and underscores the importance of providing effective and appropriate treatment, as well as implementing regular clinical and laboratory monitoring. Given that these factors and implementing routine control measures, the efforts can be made to effectively manage and control the spread of Gonorrhea [10]. Failure to cure Gonorrhea (GO) rarely occurs due to therapy failure, but it is more commonly attributed to reinfection resulting from challenges in providing therapy to sexual partners or engaging in sexual activity with a newly infected partner. This highlights the importance of education and therapy for sexual partners to minimize transmission and prevent the emergence of resistant N. gonorrhoeae strains. Further research should explore additional aspects, such as the patient’s occupation and its potential role as a risk factor for contracting sexually transmitted diseases, the side effects of therapy, and the development of antibiotic resistance. This study aims to provide valuable insights into the factors associated with dual therapy in GO patients at Dr. Soetomo Academic Teaching Hospital in Surabaya since 2017 to 2021. The hypothesis is that there is a relationship between the selection of the appropriate drug, therapy adherence, sexual abstinence, control measures, and successful recovery through dual therapy. In addition, the study seeks to examine the association between two or more risk factors and recovery rates in patients undergoing dual therapy.

Materials and Methods

The study employed an analytic observational design with a retrospective cross-sectional approach at the Sexual Transmitted Diseases Division Outpatient Clinic of Dr. Soetomo Public Academic Hospital in Surabaya during the period of 2017-2021. The objective was to analyze the relationship between various factors related to the cure of Gonorrhea patients undergoing multiple therapy. The study utilized secondary data extracted from the Electronic Medical Record (EMR) and employed bivariate analysis with the chi-square test. Ethical clearance for the study was obtained from the Ethical Committee of Dr. Soetomo Public Academic Teaching Hospital in Surabaya (Ethical Clearance No.: 0944/LOE/301.4.2/VI/2022).

Results and Discussion

Out of a total of 109 Gonorrhea patients, 64 patients met the criteria for inclusion in this study. The remaining 45 patients were excluded from the analysis due to not receiving dual therapy or not having at least one post-therapy follow-up. The analysis revealed a significant relationship between sexual abstinence and the cure of Gonorrhea patients, with a p-value of 0.001 (<0.05). Patients who practiced sexual abstinence during therapy were found to be 26 times more likely to recover compared to those who did not abstain from sexual activity (95% CI = 3.9-170).

Table 1 presents the data on the number of new Gonorrhea (GO) patients at the STI Division, Dermatology and Venereology Department of Dr. Soetomo Public Academic Teaching Hospital, Surabaya, from 2017 to 2021. During this period, 109 new GO patients accounted for 3.09% of the total patient visits in the STI Division. The highest number of visits occurred in 2018, with 28 patients, while the lowest number of visits was recorded in 2020, with ten patients.

Table 2 lists the distribution of new Gonorrhea (GO) patients who met the study inclusion criteria at the STI Division, Dermatology and Venereology Department of Dr. Soetomo Public Academic Teaching Hospital, Surabaya, from 2017 to 2021. The study inclusion criteria required patients to receive dual therapy and undergo a post-therapy control at least once, with a post-therapy control period of at least seven days. Of the total 109 GO patients, 64 (58.7%) fulfilled these criteria.

Table 3 provides the distribution of Gonorrhea patients at the STI Division, Dermatology and Venereology Department of Dr. Soetomo Public Academic Teaching Hospital in Surabaya (2017-2021). Among the included patients, 57 (89.1%) were declared cured after anamnesis, physical examination, laboratory tests, double therapy,
and education on healing factors. However, seven patients (10.9%) did not recover during the follow-up control. 

Table 4 indicated the distribution of Gonorrhea patients and factors contributing to non-recovery at the STI Division, Dermatology and Venereology Department of Dr. Soetomo Public Academic Teaching Hospital Surabaya from 2017 to 2021. Out of the total cases, seven patients did not recover. In the cefixime therapy group (400 mg + doxycycline 2×100 mg), all cases occurred in 2017 (4 cases), with 1 case each in 2018 and 2020. In the cefixime 400 mg + doxycycline 2×100 mg (PO) therapy group, there was only 1 case in 2018. Factors influencing subsequent recovery included sexual abstinence. Among those who did not practice sexual abstinence, 3 cases were reported in 2017 and 2 cases in 2018. In contrast, among those who practiced sexual abstinence, 1 case was reported in 2017 and 1 case in 2020. No other cases of non-recovery were attributed to factors such as adherence to therapy, proper medication, and routine control. 

Table 5 demonstrates that no significant relationship was found between 2 or more risk factors and the cure rate in dual therapy, preventing the possibility of conducting a multivariate analysis. The analysis of the relationship between the type of dual therapy and the cure rate yielded insignificant results (p-value = 0.664), indicating that both types of dual therapy were equally effective in achieving a patient cure. However, the analysis revealed a significant relationship between sexual abstinence and the cure rate (p-value = 0.001).

**Table 1**: Distribution of new Gonorrhea (GO) patients at the STI Division, Dermatology and Venereology Department, Dr. Soetomo Public Academic Teaching Hospital, Surabaya, from 2017 to 2021

<table>
<thead>
<tr>
<th>New Patient</th>
<th>Years</th>
<th>Amount (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>STI Division</td>
<td>2017 n (%)</td>
<td>2018 n (%)</td>
</tr>
<tr>
<td>Gonorrhea</td>
<td>26/914 (2.84)</td>
<td>28/799 (3.5)</td>
</tr>
</tbody>
</table>

**Table 2**: Distribution of new Gonorrhea (GO) patients meeting study inclusion criteria in the Sexual Transmitted Diseases Division Outpatient Clinic of Dr. Soetomo Public Academic Hospital, Surabaya, from 2017 to 2021

<table>
<thead>
<tr>
<th>Inclusion Criteria</th>
<th>Years</th>
<th>Amount (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Double therapy and 1x post-therapy control</td>
<td>2017 n (%)</td>
<td>2018 n (%)</td>
</tr>
<tr>
<td></td>
<td>17 (65.4)</td>
<td>14 (50)</td>
</tr>
</tbody>
</table>

**Table 3**: Distribution of Gonorrhea patients based on clinical at the STI Division, Dermatology and Venereology Department, Dr. Soetomo Public Academic Teaching Hospital, Surabaya, from 2017 to 2021

<table>
<thead>
<tr>
<th>Recovery</th>
<th>Year</th>
<th>Total (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2017 n (%)</td>
<td>2018 n (%)</td>
</tr>
<tr>
<td>Recover</td>
<td>13/17 (76.5)</td>
<td>12/14 (85.7)</td>
</tr>
<tr>
<td>Do not recover</td>
<td>4/17 (23.5)</td>
<td>2/14 (14.3)</td>
</tr>
<tr>
<td>Total</td>
<td>17 (100)</td>
<td>14 (100)</td>
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</tbody>
</table>
### Table 4: Factors contributing to incurability

<table>
<thead>
<tr>
<th>Factors Leading to Non-Recovery</th>
<th>Year</th>
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</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2017 n (%)</td>
<td>2018 n (%)</td>
<td>2019 n (%)</td>
<td>2020 n (%)</td>
<td>2021 n (%)</td>
<td>Total (%)</td>
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<tr>
<td>1. Therapy: Sweden &lt;br&gt; - Cefixime 400mg + Doxycycline 2×100mg (PO)</td>
<td>4/4 (100)</td>
<td>1/2 (50)</td>
<td>0/0 (0)</td>
<td>1/1 (100)</td>
<td>0/0 (0)</td>
<td>6/7 (85.7)</td>
<td></td>
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<tr>
<td></td>
<td>- Cefixime 400 mg + Azithromycin 1g (PO)</td>
<td>0/4 (0)</td>
<td>1/2 (50)</td>
<td>0/0 (0)</td>
<td>0/1 (0)</td>
<td>0/0 (0)</td>
<td>1/7 (14.7)</td>
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<tr>
<td>2. Sexual abstinence: Sweden &lt;br&gt; - Do not perform sexual abstinence</td>
<td>3/4 (74)</td>
<td>2/2 (100)</td>
<td>0/0 (0)</td>
<td>0/1 (0)</td>
<td>0/0 (0)</td>
<td>5/7 (71.4)</td>
<td></td>
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<tr>
<td></td>
<td>- Perform sexual abstinence</td>
<td>1/4 (25)</td>
<td>0/2 (0)</td>
<td>0/0 (0)</td>
<td>1/1 (100)</td>
<td>0/0 (0)</td>
<td>2/7 (28.7)</td>
<td></td>
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<tr>
<td>3. Adhere to therapy</td>
<td>0/4 (0)</td>
<td>0/2 (0)</td>
<td>0/0 (0)</td>
<td>0/1 (0)</td>
<td>0/0 (0)</td>
<td>0/7 (0)</td>
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<tr>
<td>4. Appropriate medication</td>
<td>0/4 (0)</td>
<td>0/2 (0)</td>
<td>0/0 (0)</td>
<td>0/1 (0)</td>
<td>0/0 (0)</td>
<td>0/7 (0)</td>
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<tr>
<td>5. Control</td>
<td>0/4 (0)</td>
<td>0/2 (0)</td>
<td>0/0 (0)</td>
<td>0/1 (0)</td>
<td>0/0 (0)</td>
<td>0/7 (0)</td>
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</tbody>
</table>

### Table 5: Factors associated with dual therapy cure in Gonorrhea Patients at the STI Division, Dermatology and Venereology Department, Dr. Soetomo Public Academic Teaching Hospital, Surabaya, from 2017 to 2021

<table>
<thead>
<tr>
<th>Variable</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dual therapy</td>
<td>0.664</td>
</tr>
<tr>
<td>Sexual abstinence</td>
<td>0.001</td>
</tr>
</tbody>
</table>

The findings of this study indicate that Gonorrhea patients accounted for 3.09% of the total patients at the STI Division, Dermatology and Venereology Department, Dr. Soetomo Public Academic Teaching Hospital, Surabaya. Likewise, a retrospective study by Pitasari (2019) and Puspitorini (2017) reported a decrease in the number of new Gonorrhea cases, supporting the possibility that increased access to health information through various sources such as the Internet, friends, private clinics, private doctors, or health centers may have contributed to this decline [11, 12].

In this study, it was observed that all Gonorrhea patients demonstrated full adherence to therapy in terms of dosage, frequency, and duration. Among the patients, 57 (89.1%) achieved recovery, while 7 (10.9%) did not respond to the treatment. Although the analysis of patient adherence could not be performed due to the high compliance rate, it is important to highlight that adherence to medication is a crucial aspect in the treatment of sexually transmitted infections. Proper diagnosis, selection, and administration of the appropriate medication by healthcare providers alone are insufficient to ensure treatment success. Patient adherence to take medication is essential for the therapy effectiveness.

Appropriate therapy was successfully achieved in 100% of the patients included in this study. Among them, 57 patients (89.1%) achieved complete recovery, while seven patients (10.9%) did not show signs of cure. The accuracy of indication, dosage, and administration method played a significant role in determining the treatment outcomes. It is important to note that the Gonorrhea treatment can be challenging due to the increasing resistance of Neisseria gonorrhoeae to various antimicrobials, such as sulphanilamide, penicillin, tetracycline, fluoroquinolones, and the reduced sensitivity to ceftriaxone and cefixime in certain [13, 14]. To combat this, dual therapy involving the use of two antimicrobials with different mechanisms, such as cephalexin or azithromycin or
doxycycline, has been recommended by the CDC since 2010. This approach has shown increased effectiveness and reduced susceptibility to antimicrobial resistance [13]. In addition, dual therapy can effectively treat co-infections with C. trachomatis, which are commonly observed in Gonorrhea patients. Several studies have reported the susceptibility of cephalosporins, particularly cefixime, highlighting the higher efficacy of dual therapy in such cases [6].

During the 2017-2021 period at the Sexual Transmitted Diseases Division Outpatient Clinic of Dr. Soetomo Public Academic Hospital in Surabaya, a total of 64 Gonorrhea patients were included in the analysis. Among them, ten patients (15.6%) did not practice sexual abstinence during therapy, while 54 patients (84.4%) did practice abstinence. Among the patients who practiced abstinence, 57 patients (89.1%) were cured, while seven patients (10.9%) did not recover. Fisher's test revealed a significant relationship between sexual abstinence and the cure of Gonorrhea (p-value = 0.001 < 0.05). Patients who practiced sexual abstinence had 26 times higher chances of cure compared to those who did not abstain from sexual activity during therapy (95% CI = 3.9-170). Following CDC recommendations, education on sexual abstinence for at least seven days after therapy is crucial to minimize STI transmission [15]. Therefore, to prevent reinfection, it is important to avoid any kind of sexual intercourse, including vaginal, oral, or anal, especially during high-risk periods, as it can hinder the healing process and lead to transmission.

The evaluation of the cure was conducted based on the Indonesian Ministry of Health's guidelines (2011) [16], which recommended a follow-up visit on the 7th day after dual therapy with doxycycline or cefixime. During this visit, the patients' treatment was assessed through laboratory tests or clinical examination to determine whether they were cured. Consistent with these guidelines, all Gonorrhea patients in this study received education from their doctors to return for a follow-up visit within 5-7 days after treatment. Since all patients attended the scheduled follow-up visits, the evaluation could not be performed, but it resulted in 57 patients (89.1%) being cured and seven patients (10.9%) not recovering from clinical Gonorrhea. The study identified 7 cases of patients who did not recover, indicating non-recovery. Among these cases, 4 (100%) patients received cefixime therapy of 400 mg combined with doxycycline 2×100 mg in 2017, while 1 (50%) patient each was observed in 2018 and 2020. No such cases were reported in 2019 and 2021. Furthermore, in the group receiving cefixime 400 mg + doxycycline 2×100 mg (PO), only 1 (50%) patient case was found in 2018.

**Conclusion**

The potential increase in resistance to Gonorrhea treatment is expected to persist, as indicated by previous research [17]. To mitigate the development and spread of resistance, it is crucial to focus on minimizing transmission and implementing strategies related to cures. A comprehensive approach is necessary, encompassing appropriate medication, adherence to therapy, sexual abstinence during treatment, and regular follow-up visits. Patients who abstained from sexual activity during therapy had significantly higher chances of cure compared to those who did not abstain (95% CI = 3.9-170). In line with this, the CDC recommends educating patients undergoing Gonorrhea therapy about the importance of sexual abstinence for at least seven days post-treatment to reduce STI transmission [18]. In future endeavors, maintaining comprehensive medical records becomes crucial for effective management. Patients should receive counseling emphasizing the importance of seeking medical evaluation to minimize reinfection, treatment failure, and complications, as well as promoting safe sexual practices, addressing spiritual aspects, and raising awareness about other STIs. The implementation of diverse health education models has demonstrated positive outcomes in reducing GO risk and preventing STIs relatively quickly. Moreover, education and promotion should play a significant role in counseling
In light of the aforementioned background, it is vital to refrain from engaging in any form of sexual intercourse, including vaginal, oral, or anal, to prevent reinfection. Engaging in sexual activity during high-risk periods can contribute to transmission and impede the healing process. It is important to note that no significant relationship was found between two or more risk factors and cure rates in dual therapy.

Disclosure Statement

No potential conflict of interest was reported by the authors.

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This study has been approved the Ethics Committee of Dr. Soetomo Public Academic Teaching Hospital Surabaya (No.: 0944/LOE/301.4.2/VI/2022).

Authors' Contributions

All authors contributed to data analysis, drafting, and revising of the paper and agreed to be responsible for all the aspects of this work.

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