Usefulness and Utility of NACO Regime in the Management of Sexually Transmitted Infections: A Pilot Study

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Abstract

Introduction: Treatment of sexually transmitted infections (STIs) has been made easy for field workers due to syndromic approach. The etiological agent responsible for different STI syndromes needs to be validated from time to time so as to guide the therapeutic regimen. Aims and Objectives: The aim of this study was to evaluate the etiological agent for STI syndromes and correlate the syndromic diagnosis with etiological diagnosis. Materials and Methods: The study was conducted over 9 months in all patients attending the STI and Gynaecology Outpatient Department. Syndromic diagnosis was done by STI-trained medical officer of respective clinic. Sample was collected for etiological diagnosis and subjected to relevant investigations. Data were analyzed by applying statistical methods. Results: Among 308 patients (male:female = 1:3.5), no syndromic diagnosis could be made in 11 cases (all females and had premalignant changes on Pap smear). In 68 patients (22.08%), no etiological diagnosis could be arrived at (mostly genital ulcer disease [GUD]-herpetic [H] and vaginal discharge). In cervical discharge syndrome, six patients (16.7%) showed gonococcus. In GUD-H syndrome, 37 patients (27.027%) were tested positive. In GUD-nonherpetic syndrome, three patients (33.33%) were syphilis, granuloma inguinale, and chancroid (1 each). In urethral discharge syndrome, etiology could not be found in 33 cases (45.45%). In vaginal discharge syndrome (n = 217), etiologies were overlapping as follows: trichomonas vaginalis (76.04%), bacterial vaginosis (40%), gonococcus (24%), and undiagnosed (6.5%). Conclusion: The present tool for validation of GUD-H can validate only 27% of cases. Overlap of etiologies is mostly common in vaginal discharge syndrome, wherein malignancies and premalignant conditions are overtreated with kits. Validation can be done only in two-third of cases with the available resources. However, syndromic approach provides the opportunity of treating STI without delay.

Key Words: Etiological diagnosis, sexually transmitted infections, syndromic approach

What was known?
Sexually transmitted infections (STIs) constitute a major cause of concern to the country, in terms of health, development and economy. World Health Organization has placed emphasis on syndromic approach to manage STI. It is a simple, cost-effective and comprehensive approach. However, it has its own disadvantages. In a country like ours, economic burden of STI management programs must be given top priority. It has been found that the syndromic approach leads to overtreatment in many cases and therefore, we need to assess and analyse the functioning of the system.

Introduction
Sexually transmitted infections (STIs) are a significant cause of concern to the health, social, and economic scenario of any country, including ours. Most of the STIs are prevalent in India, thus posing a serious threat to the upliftment of our country. The incidence and prevalence of different STIs depends on the socioeconomic, cultural, geographic, and environmental factors prevalent in different parts of India.1-4 However, in a developing country, financial constraints and unavailability of infrastructural facilities play a pivotal role in the management of this group of diseases.

The nonspecific signs and symptoms of various STIs, along with the prevalence of mixed infections, make precise clinical diagnosis difficult. Laboratory-confirmed etiological diagnosis is considered rational and scientific

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by many medical professionals. However, this method has its own pitfalls. Unavailability of many facilities in a resource-poor country puts a question mark to the utility of the etiological approach in the management of STIs. The World Health Organization has placed emphasis on syndromic approach.\[^{[3]}\] It provides a useful mechanism for STI services to be integrated in every nooks and corners of the country. It is a simple and rapid problem-oriented approach. Most importantly, it avoids delay in the diagnosis and treatment of STIs. Being cost-effective, it has the merit of catering to a huge coverage of population. However, every coin has two sides. Moreover, this syndromic approach is also not free of disadvantages. The system needs to adapt to specific settings, and in many cases, it leads to overtreatment, thus increasing the economic burden of the STI management programs. Therefore, continuous analysis of risk assessment and prevalence-based screening studies are quintessential to keep a check on the performance of syndromic management.\[^{[4]}\] With this background, this study was undertaken in a regional STI referral center where we intended to identify the etiological agent of various STI syndromes and validate the syndromic diagnosis.

Materials and Methods
A cross-sectional observational study was carried out in a tertiary care institute of eastern part of India. The study was approved by the Institutional Ethics Committee. Clients attending reproductive tract infection (RTI)/STI (Suraksha) clinic of the hospital constituted the study population. Participants were recruited for 9 months after obtaining informed consent. The clinic caters to the RTI/STI clients attending the institution. They are either direct walk-in clients or referred by other departments or hospital or targeted intervention nongovernmental organization. Syndromic diagnosis was documented by trained medical officers for each client by appropriate history taking and clinical examination. Biological samples linked to the individual clients were collected following standard operating procedure developed by the National Aids Control Organization (NACO). Laboratory confirmation was done by standard laboratory techniques, using appropriately collected specimens, according to clinical presentations.\[^{[4]}\]

All the samples were tested in Regional STI Referral laboratory, Kolkata. Laboratory investigations that were done for different syndromic diagnoses of STI cases are shown in Table 1.

Statistical analysis
Quantitative data were expressed as percentage and analyzed using the Chi-square test. \( P \leq 0.05 \) was regarded as statistically significant. After analysis, the results were compared with the standard data, available in the literature. Medcalc version 10.2 (Mariakerke, Belgium: MedCalc Software, 2011) was used for the same.

Results
Three hundred and eight patients attended the outpatient department (OPD) of Gynaecology and Sexually Transmitted Diseases of our Institute, over a period of 9 months (April–December, 2013). Of these patients, 11 were excluded from the study because they had presented with nonspecific complaints and could not be categorized into a particular STI syndrome. Thus, our sample size was 297. Females \((n = 229)\) outnumbered males \((n = 68)\). Most of the patients were from urban background. The patients presented to both Gynaecology and STD OPDs, with the proportion being higher for the former one. The mean age at presentation was 32.84 ± 9.63 years. Among the females, vaginal discharge was the most common syndrome \((n = 217)\), followed by cervical discharge \((n = 6)\) and genital ulcer disease (GUD)-herpetic \((H)\) \((n = 4)\). One case had both GUD-H and vaginal discharge. Among males, GUD-H \((n = 33)\) and urethral discharge \((n = 33)\) constituted the major fractions. No cases of lower abdominal pain and inguinal bubo were reported [Table 2].

In case of cervical discharge syndrome, only one out of six cases \((16.7\%)\) could be validated etiologically, which was due to Neisseria gonorrhoeal infection [Tables 3 and 4]. With the available investigatory procedures, 10/37 cases \((27.027\%)\) of GUD (herpes simplex virus-II) could be validated, after antibody testing. Besides, one patient \((2.7\%)\) had laboratory features of serological herpes virus infection [Tables 3 and 5]. On the other hand, validation could be done in 100% of cases of GUD-nonherpetic \((NH)\) (one case each of syphilis, granuloma inguinale, and chancroid) [Tables 3 and 6]. However, 18/33 cases \((54.55\%)\) of urethral discharge syndrome could be validated, which was again caused by gonococcal infection manifested as Gram-negative diplococci. Nearly 33.3% of patients had nonspecific laboratory features. About 6.06% of patients showed serological scarring. However, 3.03% of cases were actually suffering from chancroid, and subprepuical discharge was diagnosed as urethral discharge syndrome [Tables 3 and 7]. Thus, the results of validation were poor mainly in cervical discharge and urethral discharge syndromes. Among the patients who were diagnosed with vaginal discharge syndrome, 165 patients \((76.04\%)\) were diagnosed with trichomonas vaginalis infection, 87 \((40.09\%)\) with bacterial vaginosis \((BV)\), and 15 \((6.91\%)\) with candidiasis. Seven patients \((3.23\%)\) had nonspecific laboratory features. Fourteen patients \((6.45\%)\) were found to have serological scar of syphilis and two patients \((0.92\%)\) were suffering from syphilis [Tables 3 and 8].
To determine infection of T. vaginalis, one vaginal swab was used to make a thin smear in one drop of normal saline over a clean glass slide and observed microscopically under ×40 within 5-8 min of collection. Another swab was inoculated in Kuperberg medium, incubated at 37°C and observed for motility up to 7 days.[10] Vaginal swabs were taken for identification of Candida spp. and BV. For microscopic analysis (by KOH wet mount), swabs were collected and cultivated in specific SDA plate which was incubated at 25°C for 24-48 h for emergence of typical cream-colored large colonies. For further confirmation, Gram staining was done on smear from colonies for morphological identification of Candida spp. (standard operating procedures, NACO, 2012). For BV, interpretation of vaginal Gram-stained smear following Nugent’s criteria was performed.[13]

Pap smear: A sample of cells was collected from the outer opening or os of the cervix by scraping it with an Aylesbury spatula. The cells were placed on a glass slide and stained using the Pap technique. Following this, examination under microscope used to be done.

Lesions were cleaned, and the adherent mucosa was scraped with a sterile scalpel. Smear was prepared and stained with Giemsa for microscopic examination. MNGCs confirmed a diagnosis of herpes genitalis (HSV-2), and Donovan bodies were conclusive for Calymmatobacterium granulomatis infection. For antigen detection of HSV-II, IgM ELISA (Quiplo Diagnostics, Verna Industrial Estate, India) was performed. Other serological tests such as HBsAg and HCV were done by ELISA to confirm hepatitis B and hepatitis C viral infections. The sensitivity and specificity for the tests were 100%. For in vitro diagnosis, ELISA was performed by ELISA procedure of serum samples for the determination of IgM antibodies of CMV. Sensitivity was >98% and specificity was >98% on serum samples of CMV.

Blood was collected from all the attendees. Serum was separated and tested for syphilis, HSV II, HBsAg, HCV, and CMV. Tests for syphilis included VDRL test which is slide flocculation test (VDRL antigen manufactured at Institute of Serology, Kolkata). This was followed by TPHA with TPHA test Kit (New Market Laboratories Ltd, Kentford, CB8 7PN, UK) performed in VDRL-positive cases.

| Table 2: Cross-tabulation of age, sex, and clinical attendance |
|-----------------|-----------------|-----------------|-----------------|
| Syndrome        | Age (mean±SD)   | Sex (male:female) | Clinical attendance |
| VD              | 31.2±28.38      | 0.2:17           | 1:1.17           |
| CD              | 54±6.4          | 0:6              | 1:5              |
| GUD-H           | 38.8±9.63       | 33:4             | 17.5:1           |
| GUD-NH          | 41.3±11.55      | 2:1              | 2:1              |
| UD              | 28.2±7.78       | 33:0             | 33:0             |
| UD + GUD-H      | 21              | 0:1              | 1:0              |
| Others          | 46.7±5.31       | 0:11             | 1:4.5            |
| Total           | 32.8±4.93       | 1:3.5            | 1.3:1            |

VD: Vaginal discharge, CD: Cervical discharge, GUD-NH: Genital ulcer disease-nonherpetic, GUD-H: Genital ulcer disease-herpetic, UD: Urethral discharge, SD: Standard deviation

Discussion

There is conflict of data regarding the statistics of STIs in India for many reasons such as changing scenario and spectrum of the diseases, increasing trend of viral STIs, reducing prevalence of bacterial STIs, stigma and discrimination associated with the STI, and availability of limited diagnostic facilities. Our study throws some light on the current status of STIs in India and the advantages and disadvantages of syndromic approach toward the management of STIs. In GUD-H syndrome, only 10/37 cases could be confirmed etiologically and in one case had laboratory features of serological herpes, thus putting a question mark on the antibody-based diagnostic techniques. However, all the patients who were diagnosed with GUD-H syndrome were treated as per the recommendations given by the NACO. With this background, we propose to include antigen-based detection tests and nucleic acid amplification tests for the diagnosis of GUD-H syndrome. This way, we shall be able to channelize the economic resources toward a more valuable and contributory investigatory procedure. In GUD-NH syndrome, 100% validation was possible, but we still need to remain vigilant about the
syndromic diagnosis because we had found only three cases with this syndrome and this particular syndrome needs to be explored further, with a larger sample size. Urethral discharge syndrome validation was poor. In 45% of cases (15/33), we could not reach an etiological diagnosis and this gray zone needs further exploration.

Of the 217 cases of vaginal discharge syndrome, etiology could be found (partially) in 196 cases, but there was a significant proportion of patients who were suffering from multiple etiologies. Thus, repeated and periodic training of health-care professionals involved in STI programs is essential to avoid misdiagnosis. Moreover, we also found patients of syphilis presenting with vaginal discharge, which is a rare presentation of the great imitator (syphilis). This further reinforces the fact that routine Venereal disease research laboratory test is a must in all cases presenting to the STI clinic with any sign or symptom. According to a study conducted by Choudhry et al., 24% of females accounted for laboratory-positive syphilis, 19% had gonorrhea and chlamydia each, 13% had trichomoniasis, and only 5% had candidiasis.[10] Vishwanath et al. concluded in their study that the prevalence of BV was 26%, candidiasis was 25.4%, chlamydia infection was 12.2%, trichomoniasis was 10%, and syphilis was 2.2% in a reproductive health clinic in New Delhi.[11] In a study conducted by Chauhan et al., laboratory positivity was present in 26.1%, 2.8%, and 8.3% in BV, trichomoniasis, and candidiasis patients, respectively; while syphilis, gonorrhea, and chlamydia were diagnosed in 1.7% each.[12] In our study, laboratory positivity was present in 40.09%, 52.07%, and 6.91% in BV, trichomoniasis, and candidiasis patients, respectively. However, syphilis and gonorrhea were present in 0.92% and 23.96%, respectively. In another study conducted by Prabha et al., 33.14% of patients were found to be positive for at least one microorganism after laboratory testing, and BV was the most common finding (14%).[13] However, in our study, the most common finding was trichomoniasis (76.04%).

### Conclusion

In this ever-changing spectrum of presentation of STIs, infections due to multiple etiologies are fairly common. We can reliably depend on meticulous clinical examination for the diagnosis of GUD-H infections because laboratory investigations do not seem to be promising for this purpose. In this regard, it can be rightly said that we can channelize the economic resources toward the laboratory diagnosis of urethral discharge syndrome, wherein we could validate only one-third of the cases. Most importantly, periodic

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**Table 3: Percentage of etiologically diagnosed cases versus undiagnosed cases**

| Syndrome       | n     | Etiologically diagnosed cases (%) | Etiologically undiagnosed cases (%) |
|----------------|-------|----------------------------------|-------------------------------------|
| CD             | 6     | 1 (16.7)                         | 5 (83.3)                            |
| GUD-H          | 37    | 10 (27.02)                       | 27 (72.08)                          |
| GUD-NH         | 3     | 3 (100)                          | 0                                   |
| UD             | 33    | 18 (54.54)                       | 15 (45.45)                          |
| UD             | 217   | 196 (90.32)*                     | 21 (9.67)                           |
| UD and GUD-H   | 1     | 1 (100)                          | 0                                   |
| Total          | 297   | 229 (77.1)                       | 68 (22.9)                           |

*Patients presenting with UD had multiple etiology syndrome. VD: Vaginal discharge, CD: Cervical discharge, GUD-NH: Genital ulcer disease nonherpetic, GUD-H: Genital ulcer disease-herpetic, UD: Urethral discharge

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**Table 4: Cervical discharge**

| Clinically diagnosed cases (n) | Gonococcus (%) | Undiagnosed (%) |
|--------------------------------|----------------|-----------------|
| 5                              | 1 (16.7)       | 5 (83.3)        |

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**Table 5: Genital ulcer disease-herpetic**

| Clinically diagnosed cases (n) | Laboratory-confirmed cases (%) | Nonspecific (%) | Serological scar of syphilis and nonspecific for herpes (%) | Serological herpes (%) |
|--------------------------------|--------------------------------|-----------------|------------------------------------------------------------|------------------------|
| 37                             | 10 (27.02)                     | 22 (59.46)      | 4 (10.81)                                                  | 1 (2.70)               |

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**Table 6: Genital ulcer disease-nonherpetic**

| Clinically diagnosed cases (n) | Syphilis (%) | Granuloma inguinale (%) | Chancroid (%) |
|--------------------------------|--------------|-------------------------|---------------|
| 3                              | 1 (33.33)    | 1 (33.33)               | 1 (33.33)     |

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**Table 7: Urethral discharge**

| Clinically diagnosed cases (n) | Gonococcus (%) | Nonspecific (%) | Subprepuclial discharge of chancroid (%) | Chlamydia (%) | Serological scar (%) |
|--------------------------------|----------------|-----------------|------------------------------------------|--------------|----------------------|
| 33                             | 18 (54.54)     | 11 (33.33)      | 1 (3.03)                                  | 1 (3.03)     | 2 (6.06)             |
training of health-care professionals involved in STI programs is essential to avoid misdiagnosis and wrong treatment.

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**Conflicts of interest**
There are no conflicts of interest.

**What is new?**
The pattern (causative organism and clinical presentation) of STIs is changing. Infections due to multiple etiologies are becoming more prevalent. We have to channelize the economic resources towards the laboratory diagnosis of all the presentations. Besides, periodic training of health-care professionals involved in STI programs is essential to avoid misdiagnosis and wrong treatment.

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### Table 8: Vaginal discharge (n=217)

| Clinically diagnosed cases | n (%) |
|---------------------------|-------|
| T. vaginalis              | 165 (76.03) |
| BV                        | 87 (40.09) |
| Candida                   | 15 (6.91) |
| Nonspecific               | 7 (3.23) |
| Serological scar of syphilis | 14 (6.45) |
| Syphilis                  | 2 (0.92) |

BV: Bacterial vaginosis, T. vaginalis: Trichomonas vaginalis

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