



Epidemiological and clinical features of syphilis in the 21st century: A seven-year observational retrospective study of outpatients

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ABSTRACT

Background: Syphilis represents a current and emerging public health problem. The number of newly diagnosed cases of syphilis ranges from 5 to 12 million worldwide each year, albeit with differences in distribution and trend.

Methods: In this study we evaluated the trend of syphilis cases in a tertiary university hospital of Southern Italy to determine whether the clinical manifestations and/or risk factors have changed over time in relation to the patient's demographic and behavioural characteristics.

Results: In our experience we observed an increase in the number of cases of syphilis especially among young people and few subjects undergo screening after at-risk sexual intercourse and/or upon medical advice.

Conclusions: About syphilis new emerging features were observed. There was a need to pay more attention to screening, prevention and information for this pathology.

1. Introduction

Syphilis is a chronic sexually transmitted infection (STI) caused by the spirochete *Treponema pallidum* subsp. *pallidum*, which still today is a common health problem.^{1,2} Indeed, although effective antibiotic treatment has been available since the mid-twentieth century, the number of newly diagnosed cases of syphilis ranges from 5 to 12 million worldwide each year,^{3–5} albeit with differences in distribution and trend.^{3,6,7}

While the incidence of syphilis dropped significantly worldwide and reached its lowest levels 5 decades after the advent of penicillin in the mid-1940s,^{8–10} an increase in the disease was reported towards the end of the 20th century in the United States,^{11–13} mostly in young people and men who have sexual activity with other men (MSM).¹⁴ At the same time, a relative increase of syphilis was reported in MSM in the member states of the European Union and in countries of the European Economic Area.¹⁵ Although in Italy, new syphilis cases must be recorded in the national register, only a minority of physicians do so.^{16,17} Consequently, the true number of cases is underestimated. In this study we evaluated the trend of syphilis cases in a tertiary university hospital of Southern Italy in the second decade of the 21st century to determine whether the clinical manifestations and/or risk factors have changed over time in

relation to the patient's demographic and behavioural characteristics.

2. Materials and methods

After a preliminary interview, all outpatients with a diagnosis of syphilis referring to the Infectious Diseases Unit of the University of Naples Federico II between May 2013 and May 2020, were asked to provide informed consent to be enrolled in the study. Inclusion criteria were: a confirmed syphilis diagnosis, adult age and the ability to give informed consent. The exclusion criteria were non-adult age and refusal to participate in the study.

Each patient completed an anonymous questionnaire regarding: i) demographic data (gender, age, nationality), ii) behavioural data (sex orientation, risk factors for STI, alcohol intake, substance abuse, smoking) and iii) clinical data (other STI diagnosis, stage of clinical syphilis infection, pregnant status in female patients). The risk factors for STI were number of sexual partners in the past 6 months, type of sexual relationship (heterosexual, homosexual, bisexual), stability of sexual relationship (monogamous partner or occasional partners including sex workers), sexual practices (vaginal, anal, oral sex), use of condom (always, occasionally, never). Patients were also required to provide

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information regarding prison sentences, tattoos, domestic violence, sexual abuse, and relationships with partners with STI.

Syphilis was diagnosed based on clinical manifestations (staphylocomas, skin lesions, lymphadenopathies, alopecia, splenomegaly and hepatomegaly) and/or standardized laboratory testing. Patients underwent two diagnostic treponemal tests namely, the quantitative treponema pallidum hemagglutination assay (TPHA) and two non-treponemal tests (NTT), namely, quantitative the Venereal Diseases Research Laboratory (VDRL) or quantitative Rapid Plasma Reagin (RPR) tests, as well as blood count, glycemia, creatinine, albumin, and screening for Human Immunodeficiency Virus (anti-HIV), Hepatitis C Virus (anti-HCV) and Hepatitis B virus (HBsAg, HBsAb, HBcAb) were prescribed.^{7,16} The serological criteria for diagnosis (in the absence of clinical manifestations) were evidence of NTT positivity in a previously NTT-negative subject or a threefold increase of NTT titre versus a previous determination together with a positive TT. Reinfection was defined an increase in NTT titre six months after recovery from the disease.

Based on clinical findings and serological tests, untreated syphilis was classified as follows: *primary syphilis* (ulcer or chancre at the infection site, painless regional lymphadenopathy and at least one reactive serological TT or NTT test); *secondary syphilis* (localized or disseminated maculo-papular eruption with or without rash on palms and soles, oral mucosal erosions, generalized lymphadenopathy and reactive NTT tests (titre ≥ 4) and reactive TT); *latent syphilis* (reactive TT and NTT tests without other evidence of disease), which can be classified “*early latent*” (in case of documented seroconversion or fourfold increase in titre of a NTT, or unequivocal symptoms of primary/secondary syphilis during the year before the patient’s evaluation; or sexual exposure to a partner with early syphilis during this time); *late latent* (seroconversion later than one year but already known) and *latent of unknown duration* (the date of initial infection cannot be established); *tertiary syphilis* and *neurological syphilis*.^{18,19}

Neurosyphilis was diagnosed based on clinical signs of the disease, a reactive serum treponemal test, and reactive VDRL in CSF or detection of *T. pallidum* DNA in CSF or tissues with polymerase chain reaction test (PCR) or identification of treponemes in tissue with silver or immunohistochemical staining or elevated CSF protein or leukocyte count in the absence of other known causes. Finally, tertiary syphilis (cardiovascular or gummatous), defined as a clinically compatible case, and reactivity of a TT or detection of *T. pallidum* in tissue with PCR or microscopy examination.

2.1. Statistical analysis

Among-group comparisons were made using the chi-squared test or the Fisher’s exact test when appropriate. The cut-off for statistical significance was set at 5% in a two-tailed test. Univariate and multivariate analyses for the evaluation of risk factors were conducted using the logistic regression function. The variables that showed a significant association at univariate analysis were included in the multivariate model analysis. The cut-off for statistical significance of the logistic regression function was set at 5%. The study had been approved by the local Ethics Committee of the University of Naples Federico II.

2.2. Patient and public involvement

Patients were involved in the design and conduct of this research. During the study, patients were informed and discussed with them on how to enroll and conduct the study. Each patient who decided to participate in the study, after signing the informed consent, was asked a questionnaire with questions regarding the study. During the interview, the co-investigators were at the patient’s complete disposal to answer and resolve any doubts raised. The enrollment of the patient involved the establishment of an interview and at the same time a friendly interview with the patient. When the results emerged, we evaluated the

results with the co-investigators and with the patients to obtain their feedback in order to be able to communicate the results as clearly as possible both to the scientific community and to the general public.

3. Results

3.1. Study population

A total of 97 subjects were enrolled during the study period: 59 (60.8%) men and 38 (39.2%) women (p : 0.072). Table 1 shows that the number of cases per-year.

The proportion of syphilis cases in men and women (male-to-female ratio M:F) is 1.5.57 out of 97 cases (58.76%) have been reported among patients ranging from 18 to 32 years, 20 cases (20.61%) between 33 and 47 years, 14 cases (14.43%) between 48 and 62 years, 5 cases (5.15%) between 63 and 77 years and lastly 1 case between 78 and 94 years (p : 0.046). (Table 1, Fig. 1).

In the 18-32-age class, which was the most numerous group, 31 of the 57 patients (54.38%) were men and 26 patients (45.61%) were women (p 0.078). Thirty nine of the 97 patients (40.20%) reported regular sexual intercourse: 28 were monogamous (71.79%) and 11 were not (28.20%). In 11 of the 28 couples (39.28%) a member of the couple was TPHA-positive. Twenty-nine of the 97 patients (29.89%) completed the section of the questionnaire related to syphilis risk factors: 17 of the 59 men (28.81%) and 12 of the 38 women (31.57%) (p 0.085). Among these 29 patients, the reported sexual behaviours were MSM in 7/17 men (41.17%), heterosexual habitus in 10 of 17 men (58.82%), whereas all 12 women declared a heterosexual habitus (p : 0.072). Twelve of these 29 patients (10 men and 2 women) reported the type of sexual intercourse: oral (10 patients), vaginal (6 patients), insertive anal (3 patients), receptive anal (2 patients) and both insertive and receptive anal (2 patients).

Of the 19 patients who completed the questionnaire regarding condom use, 10 (52.6%) never used a condom, while 4 (21.1%) always did, 2 (10.5%) sporadically, 2 almost always (10.5%), and 1 rarely (5.3%), and a condom was reportedly used only for occasional sexual intercourse with a new or unknown partner. Fifty one of the 97 patients (52.57%) reported the number of sexual partners in the 6 months before the clinical visit. Eleven of these patients (21.56%) had more than one partner or unknown partners, 30 (58.82%) had a single partner, whereas 10 patients (19.60%) did not specify the number of sexual partners. Only 13 patients (13.40%) provided information about other risk factors. Three patients had tattoos, one patient had undergone sexual abuse, 2 reported tobacco smoking, 9 reported occasional alcohol use, and former in 2 cases, and 2 reported drug use (cannabis or cannabis plus cocaine).

The reasons for referral for a medical examination were: gynecologist prescription in 22 women (22.7%), and pregnancy screening (57.9% of all female patients), symptomatic disease in 20 patients (20.6%), urologist’s prescription in 16 men (16.5%), for fertility or prostate screening (27.1% of all male patients), syphilis positivity after blood donation in 13 patients (13.4%), screening after a positive test in a partner in 13 patients (13.4%), medical advice in 6 cases (6.2%), screening after at risk sexual intercourses and/or suspected ITS in 4 (4.1%), after miscarriage in 2 women (2.1%) and follow-up for colon

Table 1
Number of cases and distribution by sex over time.

Year	2014	2015	2016	2017	2018	2019	2020
Men	2 (3.1%)	2 (3.1%)	5 (7.9%)	12 (19%)	16 (25%)	25 (39%)	1 (1%)
Women			1 (2%)	14 (41%)	8 (23%)	10 (29%)	1 (2%)
Overall	2 (3%)	2 (3%)	6 (7%)	26 (27%)	24 (25%)	35 (36%)	2 (3%)

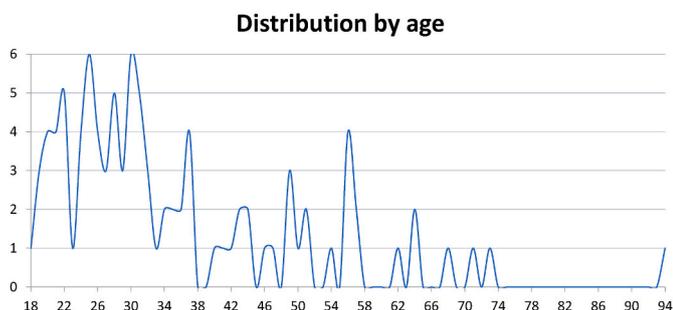


Fig. 1. Distribution of syphilis cases according to patient's age.

cancer in 1 patient (1%) (Fig. 2).

At the time of the visit, 21 women out of 38 women (55.3%) including 2 foreigners, were pregnant, 3 (7.9%) had recently delivered and 2 (5.3%) after a miscarriage; the remaining 12 women (31.5%), including the 2 foreigners) for different reasons: after blood donation (4 cases), symptomatic disease (3 cases), after prostate examination or fertility test (2 cases), after partner's positivity (2 cases) and after medical advice (1 case).

3.2. Syphilis infection

Based on clinical, anamnestic and laboratory results, subjects positive at a *T. pallidum* test were categorized as shown in Fig. 3.

Eight 8 patients (8.2%) were diagnosed with primary syphilis, 12 (12.4%) with secondary syphilis, 8 (8.2%) with early latent syphilis, 6 (6.2%) with late latent syphilis, 60 (61.9%) with latent of indefinite duration syphilis and 3 (3.1%) with neurosyphilis. At the time of the visit, lymphadenopathy and hepatomegaly were detected in 10 (10.3%) and 3 patients (3.1%), respectively.

Overall syphilis lasting less than 12 months (primary syphilis, secondary syphilis and early latent syphilis) accounted for 28 cases (28.9%), namely 5 women (17.9%) and 23 men (82.1%). Whereas syphilis lasting longer than 12 months (late latent, latent of indefinite duration syphilis and neurosyphilis) accounted for 69 cases (71.1%), namely, 33 women (47.8%) and 36 men (52.2%). Unknown latent syphilis was the most frequent diagnosis (Table 2).

Twelve of the 97 patients (12.37%) had previously been treated for syphilis (reinfection). Only one patient (1.03%) declared to have been previously diagnosed with another STI (Candida, Chlamydia and Gonorrhoea); 1 patient (1.03%) had HIV co-infection, 2 (2.06%) HBV infection (1 with HCV co-infection), while 41 patients (42.3%) are vaccinated for hepatitis B.

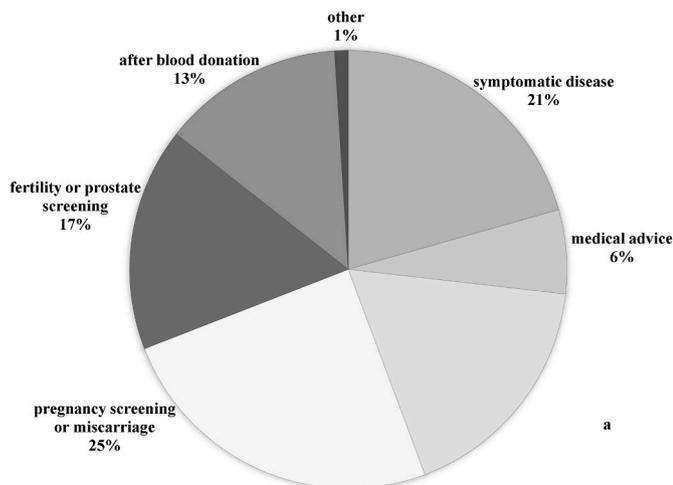


Fig. 2. Reasons for referral to the Infectious Disease Unit.

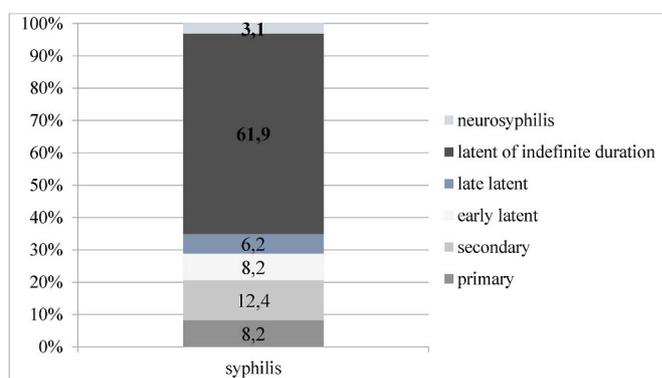


Fig. 3. Distribution of clinical forms of syphilis.

4. Discussion

It was surprising to observe the high number of new syphilis diagnoses, particularly in the three-year period 2017–2019, with the maximum peak in 2019. Although the percentage of men patients (60.8%) exceeded that of women patients (39.2%), the difference was not statistically significant ($p = 0.072$). Conversely, the percentage of patients aged between 18 and 32 years was significantly higher (58.76%) than in the age groups over 40 years ($p = 0.046$). Furthermore, there was a progressive decrease in number of patients in the older age group. Even in relation to the different age groups, there were no statistically significant gender differences.

These data coincide with the trend at national level and in the international literature.^{20–22} The data concerning nationality was also relevant, in fact almost all patients (95.87%) tested were Italian.²³ In relation to the potential risk factors for the acquisition of this infection represented by unprotected sexual intercourse among MSMs and the different sexual behaviors, no significant differences were observed. This finding differs from previous reports that in fact, currently most cases of syphilis are reported among MSM.^{14,15,24} However, this finding should be evaluated in the light of the small the sample size considered as only thirty nine of 97 patients (40.20%) indicated the type of sexual relationship and only 39 of 97 patients (29.89%) completed the section of the questionnaire regarding risk factors for syphilis infection.

In relation to the reason for carrying out serological investigations for syphilis, an important role played by screening in the gynecological and urological fields was observed. Conversely, only 17% of patients underwent screening after being exposed to a syphilis risk factor and only 6% underwent the test after physician prescription, thus showing how the screening activity for *Treponema* infection is poorly considered and as this infection is often underestimated.²⁵ In light of the fact that syphilis is often underestimated, most patients (61.9%) received the diagnosis of latent syphilis of indefinite duration and 71.1% of all patients had been infected for more than 12 months. Particularly interesting was the finding of the absence of co-infections in almost all the patients considered, in fact only 1 patient (1.03%) had HIV co-infection, 2 (2.06%) HBV infection (1 with HCV co-infection).^{26–29}

5. Conclusions

This study shows that cases of syphilis have increased in our geographical area in recent years particularly among young people. We also found that very few subjects undergo screening after at-risk sexual intercourse and/or upon medical advice. Furthermore, in our region syphilis is no longer characteristic of certain categories of people, neither is it associated with particular risk factors. This emerging scenario should alert the relevant authorities to the need for screening, prevention and information activities regarding this disease.

Table 2
Number of cases and distribution by diagnosis over the years.

Year	2014	2015	2016	2017	2018	2019	2020
Primary				2 (2.1%)	3 (3.4%)	2 (2.1%)	1 (1.2%)
Secondary			1 (1.2%)	2 (2.1%)	3 (3.4%)	6 (6.6%)	
Early latent						8 (8.5%)	
Late latent			2 (2.1%)	2 (2.1%)	2 (2.1%)		
Unknown latent	2 (2.1%)	2 (2.1%)	3 (3.4%)	20 (20.6%)	14 (14.4%)	18 (19%)	1 (1.2%)
Tertiary					2 (2.1%)	1 (1.2%)	

Availability of data and material

There is an “Availability of data and materials”.

Competing interests

There are no financial or non-financial competing interests.

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Authors' contributions

Biagio Pinchera: first author and the corresponding author.
The others authors: co-authors.

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I confirm I have provided a complete declarations section in my manuscript, in particular

- I have obtained ethic approval and consent to participate.
- I have the consent for publication
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- I have not competing interests
- I have not funding
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The undersigned declares that what has been reported has been done and is true.

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