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Ceftriaxone compared with benzylpenicillin in the treatment of neurosyphilis in France

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Abstract

Background Intravenous benzylpenicillin is the gold-standard treatment for neurosyphilis but it requires prolonged hospitalization. Ceftriaxone is a possible alternative treatment, the effectiveness of which remains unclear.

Methods We performed a retrospective multicentre study at eight tertiary care centers in France, from January 1st 1997 to December 31st 2017. Patients with neurosyphilis defined by 1) positive treponemal and non-treponemal tests and 2) otic syphilis and/or ocular syphilis and/or either neurological symptom with positive CSF-VDRL or positive CSF-PCR or >5 leukocytes on CSF cell count, were identified from medical information department database of each center and assigned to two groups on the basis of the treatment received (benzylpenicillin or ceftriaxone). The primary outcome was overall clinical response (OCR, i.e. complete and partial responses) one month after treatment initiation. The secondary endpoints were complete response (CR) at one month, serological response at six months and length of hospital stay.

Findings We included 208 patients in this study (42 in the ceftriaxone group and 166 in the benzylpenicillin group). We observed 41 OCR (98%) in the ceftriaxone group, versus 125 (76%) in the penicillin group. After propensity score weighting, OCR rates differed between the groups (OR 1.22 [1.12-1.33], $p < 0.0001$), whereas CR rates did not (OR 1.08 [0.94-1.24], $p = 0.269$). Serological response at six months did not differ between the groups (21/24 (88%) vs. 76/93 (82%), $p = 0.50$), but hospital stay was shorter for the ceftriaxone group than for the penicillin group (13.8 ± 6.4 vs. 8.9 ± 9.9 days, $p < 0.0001$).

Interpretation

Our results suggest that ceftriaxone is as effective as benzylpenicillin for neurosyphilis treatment, potentially decreasing the length of hospital stay. Randomised controlled trials should be conducted to confirm these results.

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None

1 **Introduction**

2
3 Syphilis is a sexually transmitted disease (STD) caused by *Treponema pallidum*. A
4 resurgence has been reported since the turn of the century, in high- and low-income countries,
5 as observed for other STDs, particularly among men who have sex with men (MSM). A large
6 proportion of those affected are patients living with HIV/AIDS (PLWHA). The incidence of
7 syphilis was 9.5 cases per 100,000 inhabitants in the USA in 2017,¹ and 22 cases per 100,000
8 inhabitants in China in 2008.² Neurosyphilis accounts for 1.8% to 3.5% of syphilis cases³ and
9 its diagnosis is often challenging, due to polymorphic clinical manifestations. It is strongly
10 associated with HIV infection.^{3,4} Early neurosyphilis usually presents as meningitis, cranial
11 nerve palsies, ocular and otic syphilis, whereas late neurosyphilis encompasses general paresis
12 and tabes dorsalis. Neurovascular syphilis can occur at both stages.^{3,5}

13 According to European, US and UK guidelines, the gold-standard treatment for
14 neurosyphilis is intravenous benzylpenicillin (24 M IU per day for 10-14 days).⁶⁻⁸ However,
15 this treatment requires four daily injections, potentially resulting in a long hospital stay. Few
16 data are available concerning the safety and efficacy of alternative treatments for
17 neurosyphilis that could lessen the burden of patient care and could be used in patients
18 allergic to penicillin. Ceftriaxone is active against *T. pallidum* in experimental models,⁹ has
19 intermediate diffusion in cerebrospinal fluid (CSF)¹⁰ and can be administered once daily.
20 Several studies have suggested that it is an effective treatment for neurosyphilis, but most of
21 the clinical data obtained to date originate from case reports and small studies.¹¹ Other studies
22 have mostly been limited to syphilitic uveitis¹² and PLWHA,^{13,14,15} and had unclear outcome
23 definitions, different treatment durations, and some included combination treatments.

24 If ceftriaxone proves to be as effective as benzylpenicillin, it could be used as outpatient
25 parenteral antimicrobial therapy (OPAT). This would decrease the length of hospital stay,
26 which would be beneficial both economically and in terms of the patients' quality of life.

1 In this study, we compared the effectiveness of ceftriaxone with that of the recommended
2 regimen of 14 days of benzylpenicillin for the treatment of neurosyphilis.

4 **Patients and methods**

5 *Study overview*

6 We performed a retrospective multicentre study from January 1st 1997 to December
7 31st 2017 at eight French tertiary care centers. This study conducted in accordance with good
8 clinical practice and the Declaration of Helsinki was approved by the Toulouse University
9 Hospital (RnIPH 2020-16) and covered by the MR-004 reference methodology (CNIL
10 number: 2206723 v 0). According to French law on ethics, patients were informed that their
11 codified data will be used for the study. The study was also declared to the “Institut National
12 des Données de Santé” under number MR2914170420.

14 *Study population*

15 Patients were selected from the medical information department database of each
16 center for the 1997-2017 period (CIM-10 coding A504, A521, A523). The inclusion criteria
17 were: patient over the age of 18 years, with a confirmed diagnosis of neurosyphilis.
18 Neurosyphilis was defined as: 1) ocular syphilis or otic syphilis; and/or the presence of
19 neurological symptoms associated with more than five leukocytes on CSF cell counts and/or
20 positive CSF VDRL, and/or positive CSF *Treponema pallidum* PCR; 2) at least one positive
21 treponemal test on serum, such as ELISA, FTA or TPHA, and one positive non-treponemal
22 test, such as a serological VDRL test or RPR test. All diagnoses were made by an infectious
23 diseases or ophthalmology specialist and retrospectively reviewed by AJ and TB. Patients
24 with late neurosyphilis, defined as tabes dorsalis, general paresis, dementia, parenchymatous

1 syphilis and/or negative serological VDRL tests, asymptomatic neurosyphilis or an alternative
2 diagnosis were excluded.

3

4 *Treatment groups*

5 Two groups of patients were defined on the basis of initial treatment: intravenous
6 ceftriaxone (2 g once daily) or intravenous benzylpenicillin (3-4 million units every four
7 hours). Patients had to be treated for at least 10 days to be eligible for inclusion.

8

9 *Covariables of interest*

10 We assessed clinical data from medical charts, including age, sex, HIV and
11 immunosuppression status, history of previous episodes of syphilis and other STDs. Data
12 concerning systemic glucocorticoid treatment were also collected. Neurosyphilis was
13 separated into five different subtypes according to clinical characteristics, including
14 meningitis, facial palsy, otic syphilis, neurovascular syphilis, and ocular syphilis
15 (encompassing overlapping forms, including: anterior, intermediate, posterior uveitis and
16 optic neuritis). A single patient could present with several subtypes of neurosyphilis, such as
17 ocular syphilis and meningitis, for example. Extraneurological and/or ophthalmological
18 symptoms, such as skin rash, lymphadenopathy and alopecia, were also assessed. The
19 following biological variables of interest were collected: serum VDRL or RPR titer at
20 diagnosis and six months after treatment, CSF VDRL titer at diagnosis and six months after
21 treatment, CSF cell count and CSF protein levels. Data were collected retrospectively.

22

23 *Outcomes*

24 Clinical response obtained from medical charts was assessed one month after
25 treatment initiation retrospectively by the investigators. Clinical complete response (CR) was

1 defined as the total disappearance of neurological or ophthalmological symptoms. Clinical
2 partial response (PR) was defined as a significant improvement in symptoms, without a return
3 to baseline. For uveitis, CR was defined as a total recovery of previous vision, PR as a
4 recovery of vision without reaching CR. For otic syphilis, CR was defined as a total recovery
5 of previous hearing and PR as a recovery without reaching CR. For meningitis, CR was
6 defined as a total recovery from meningeal symptoms, and PR as a recovery with sequelae.
7 For facial palsies, CR was defined as total recovery from the palsy and PR as partial recovery,
8 and, for neurovascular syphilis, CR was defined as a recovery from neurological symptoms
9 and PR as a recovery with sequelae. In the case of overlapping forms, recovery in both
10 categories was required for patients to be considered to display CR or PR. The primary
11 outcome was overall response (CR + PR) at one month after treatment initiation. Secondary
12 outcomes were CR, a four-fold decrease in serum VDRL titer six months after treatment, and
13 length of hospital stay. It was not possible to evaluate CSF control due to the small size of the
14 sample.

15

16 *Statistical analysis*

17 *Descriptive statistics*

18 Quantitative variables are reported as the median (interquartile range (IQR)) or mean
19 (standard deviation (SD)) and categorical variables are reported as numbers (percentages).
20 The ceftriaxone and benzylpenicillin groups were compared in chi-squared or Fisher's exact
21 tests, as appropriate, for categorical variables, and Student's *t*-tests or Wilcoxon-Mann-
22 Whitney tests for quantitative variables.

23 *Causal inference*

24 We initially estimated the association between treatment and clinical response with an
25 unadjusted logistic regression model. Given the variability of the baseline covariates of

1 interest, we then performed a weighted logistic regression, with inverse probability of
2 treatment weighting (IPTW method) for overall response and CR. We estimated a propensity
3 score, defined as the probability of treatment allocation conditional on measured baseline
4 covariates. Each patient's weight was equal to the inverse of the probability of receiving the
5 treatment that the patient received. This method is used to reduce the indication bias of
6 treatment allocation. A non-parsimonious multivariable logistic regression analysis was
7 performed to estimate the probability of each patient receiving ceftriaxone given their
8 baseline covariates (i.e., the propensity score of each patient). The variables included in the
9 propensity score were prespecified before outcome analysis and included center, age at
10 diagnosis, HIV status, history of previous episodes of syphilis, and clinical form of
11 neurosyphilis (i.e. uveitis, optic neuritis, labyrinthitis, meningitis, vasculitis or facial
12 paralysis). We did not include CSF VDRL in the primary analysis because 30% of patients
13 presented with missing data, which we decided not to impute. Moreover, to avoid bias, we did
14 not include systemic glucocorticoid use in the model because this treatment was always
15 initiated several days after the introduction of antibiotic treatment, mostly in cases of negative
16 outcome, and was unlinked to treatment allocation. Standardised differences were used for
17 quantitative comparisons of the baseline covariates measured between the benzylpenicillin
18 and ceftriaxone groups in the sample weighted by the inverse probability of treatment. A
19 threshold of 10% was used to assess imbalance.¹⁶

20 Patients who changed treatment regimen remained in their initial treatment group for
21 the intention-to-treat analysis. Two sensitivity analyses were performed. The first included
22 CSF VDRL in the model, and the second was a per-protocol analysis. Moreover, for the
23 assessment of response homogeneity, several subgroup analyses were also performed,
24 according to HIV status, neurosyphilis subtype and CSF leukocytosis > 5 per mm^3 . All

1 statistical analyses were performed with R software (CRAN R Project 3.6.3). All tests were
2 two-tailed, and values of $p < 0.05$ were considered significant.

3

4 *Role of the funding source*

5 This study was not funded. The corresponding author had full access to all the data in
6 the study and had final responsibility for the decision to submit for publication.

7

8

9 **Results**

10 *Study population*

11 We included 208 patients (**Figure 1**), with a median age of 47 years (IQR: 36-56) in
12 this study: 193 (93%) were men and 102 (49%) were PLWHA. The PLWHA included 99
13 (97%) men. The clinical characteristics of the patients are presented in **Table 1 and**
14 **Appendix p3**. The choice of treatment was left to the clinicians caring for patients. Forty-two
15 patients were initially treated with ceftriaxone and 166 patients were initially treated with
16 benzylpenicillin. In total, 67 (40%) patients from the benzylpenicillin group and 14 (33%)
17 from the ceftriaxone group presented with signs of secondary syphilis, such as eruptions,
18 affected lymph nodes, or both. The two groups differed principally in terms of the clinical
19 type of neurosyphilis ($p=0.006$), with uveitis more frequent in the benzylpenicillin group
20 (55%) than in the ceftriaxone group (33%). Similarly, a higher proportion of the patients in
21 the benzylpenicillin group had positive CSF VDRL results (42% vs. 28%, $p=0.05$), which
22 may have influenced the choice of treatment. CSF *Treponema pallidum* PCR was performed
23 on 32 patients and was positive for seven (22% 1/4 in the ceftriaxone group and 6/28 in the
24 penicillin group). During the study, 38 patients (23%) initially treated with benzylpenicillin
25 were switched onto ceftriaxone, after a median of 7 days (IQR: 5-12), but these patients were

1 kept in the benzylpenicillin group for the intention-to-treat analysis. This group consisted of
2 16 patients with uveitis, 14 with otic syphilis, six with meningitis, and two with facial palsies
3 but no patients with neurovascular syphilis. Conversely, none of the patients initially treated
4 with ceftriaxone were switched onto benzylpenicillin. The median duration of treatment was
5 14 days (IQR:14-14, range: 10-21 days) for each group.

6

7 *Propensity score*

8 Median propensity score was 0.10 (IQR: 0.00-0.18) in the benzylpenicillin group and
9 0.54 (IQR: 0.25-0.58) in the ceftriaxone group. ($p<0.001$) (**Appendix p5**). The C statistic of
10 the model was 0.88 (95% CI: 0.82-0.92). After application of the IPTW method, 16 of the 17
11 variables included had a standardised mean difference below 10% (**Appendix p6**). The
12 threshold was exceeded, and even then only slightly (10.3%), for optic neuritis, due to its
13 higher prevalence in the ceftriaxone group. We nevertheless retained this variable in the
14 model because we considered it to be a subvariable of the clinical form of neurosyphilis.

15

16 *Endpoints*

17 The primary and secondary endpoints are presented in **Table 2**. In total, 41 overall
18 clinical responses (98%) were observed in the ceftriaxone group, versus 126 (76%) in the
19 benzylpenicillin group (crude OR 13.02 [1.73-97.66], $p=0.02$). This difference persisted after
20 propensity score weighting (OR 1.22 [1.12-1.33], $p<0.0001$). Likewise, 22 complete
21 responses (52%) were observed in the ceftriaxone group, versus 55 (33%) in the
22 benzylpenicillin group (crude OR 2.26 [1.12-4.41], $p= 0.03$). However, this difference was
23 not significant after propensity score weighting (OR 1.08 [0.94-1.24], $p=0.269$). Consistent
24 results were obtained for the sensitivity analyses (**Table 2**). For the subgroup of 38 patients
25 switched from benzylpenicillin to ceftriaxone, 32 (84%) presented an overall clinical response

1 and 17 (45%) presented a CR. Serological responses at six months did not differ between the
2 groups (88% vs. 82%, $p=0.50$), but patients were hospitalized for a shorter length of time in
3 the ceftriaxone group than in the benzylpenicillin group (13.8 ± 6.4 vs. 8.9 ± 9.9 days,
4 $p<0.0001$). Subgroup analyses according to HIV status, neurosyphilis subtype and CSF
5 leukocytosis revealed no differences in complete response rates between groups (**Figure 2**).
6 Given the small size of the groups, neurovascular syphilis and facial palsies were grouped
7 with meningitis. It was not possible to calculate the OR for overall response in the different
8 subgroups, due to a lack of events. Absolute values and percentages are provided in
9 **Appendix p4**. No major adverse effects were reported in either group.

10

11 **Discussion**

12 In this study, ceftriaxone was found as effective as the gold-standard, benzylpenicillin,
13 for the treatment of neurosyphilis, according to the rates of complete clinical response at one
14 month and serological response at six months, and the use of ceftriaxone was associated with
15 a shorter stay in hospital.

16

17 A prospective study considering all forms of syphilis has already reported a better
18 serological response to ceftriaxone at a dose of 1 g daily for 10 days than for two weekly
19 injections of benzathyl-benzylpenicillin,¹⁷ but a meta-analysis reported an absence of
20 difference between ceftriaxone and penicillin.¹⁸ Focusing on neurosyphilis, *T. pallidum*
21 probably invades the CNS early on, as *T. pallidum* is isolated in the CSF of 30% of patients
22 with primary and secondary syphilis.¹⁹ Relapses of neurosyphilis have been shown to occur
23 after benzathine penicillin treatment, particularly among PLWHA,^{4,20} but the risk of
24 developing symptomatic neurosyphilis is unknown, and there is no evidence available to
25 determine whether asymptomatic neurosyphilis is predictive of treatment failure.²¹

1 Ceftriaxone has similar and intermediate CSF diffusion features to benzylpenicillin in
2 uninflamed and inflamed meninges,¹⁰ and may therefore be considered to offer a good
3 alternative to benzylpenicillin.²⁰ Focusing on neurosyphilis, a few studies have reported
4 ceftriaxone to be effective in PLWHA¹⁴ and in patients with uveitis,¹² with response rates of
5 80% and 67%, respectively, but US and UK guidelines are not in line with European
6 guidelines concerning the use of ceftriaxone.⁶⁻⁸ Our subgroup analyses were consistent with
7 these previous findings. However, as the number of patients in each subgroup was small, the
8 results must be interpreted with caution, without extrapolation beyond a general homogeneity
9 of the results. Thus, our results support the use of ceftriaxone as an alternative to
10 benzylpenicillin for the treatment of neurosyphilis, several potential benefits. First, for
11 patients allergic to penicillin, a penicillin desensitization treatment regimen is often
12 recommended, but this delays syphilis treatment, which may have negative consequences. For
13 such patients with no contraindication to cephalosporins, particularly in the absence of cross
14 allergy, ceftriaxone may be an appropriate first-line treatment. Second, once-daily ceftriaxone
15 is already widely and safely used in OPAT programmes.²² Selected patients with
16 neurosyphilis ready for hospital discharge are therefore potential candidates for the
17 completion of OPAT with ceftriaxone, which would greatly decrease costs and improve
18 quality of life.²³ However, these advantages must be weighed up against the broader
19 antimicrobial spectrum of ceftriaxone, resulting in a higher ecological burden on microbiota,
20 and a higher risk of the emergence of antibiotic resistance and *Clostridioides difficile*
21 infection.²⁴

22 There is still no consensus definition of neurosyphilis, and its diagnosis remains
23 challenging. In this study, we chose to exclude cases of asymptomatic neurosyphilis, because
24 treatment is not consensual, clinical outcome is difficult to assess, and CSF abnormalities are
25 likely to resolve with classical treatment for secondary syphilis.^{3,5} The sensitivities of CSF-

1 VDRL, and CSF-PCR for the diagnosis of neurosyphilis have been estimated at 30-70%,²⁵
2 and 6-77%, respectively.²⁶ Moreover, although CSF pleocytosis is a marker of meningitis,³
3 CSF examination may be normal in up to 30% of ocular syphilis²⁷ and 90% of otic syphilis
4 cases.²⁸ A diagnosis of neurosyphilis cannot, therefore, be ruled out on the basis of a normal
5 CSF examination. However, positive findings on clinical examination associated with positive
6 treponemal and non-treponemal tests remain strongly suggestive of neurosyphilis. In this
7 study, more than a third of patients presented with clinical signs of secondary syphilis.
8 Therefore, given the challenging nature of neurosyphilis diagnosis, careful screening for
9 extraneurological signs is warranted.

10

11 The strengths of this study are its sample size, with the inclusion of patients from eight
12 referral centers in France, and the use of a propensity score. However, this study is also
13 subject to several limitations, particularly its retrospective design and the indication bias of
14 treatment allocation. The sample size, although relatively large for this rare condition, may
15 not be enough to draw any definitive conclusions. The use of a weighted propensity score
16 partially corrects this bias, but cannot replace randomization. Our results suggest that the use
17 of ceftriaxone is associated with shorter hospital stay, but we cannot exclude the possibility
18 that the patients in the benzylpenicillin group suffered from more severe disease, necessitating
19 a longer stay in hospital regardless of treatment. Moreover, almost all the patients in our study
20 were men, and 49% were PLWHA, consistent with findings for the current European
21 endemic,²⁹ but very different from Asian or African reports,^{30,31} limiting the generalizability
22 of our results to other countries. Finally, the retrospective design of this study precluded an
23 analysis of the adverse effects associated with the use of ceftriaxone.

24

1 In the context of the current rapid reemergence of syphilis, this study suggests that
2 ceftriaxone may be considered as a reliable alternative to benzylpenicillin for the treatment of
3 neurosyphilis. In selected patients, OPAT with ceftriaxone may make it possible to decrease
4 the length of hospital stay, reducing costs while improving quality of life for patients.
5 Randomised controlled trials are however warranted to determine the best treatment options
6 for neurosyphilis.

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11
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17
18 **Author contributions:**

19 ND and GMB designed the study
20 TB, AJ, MM and SM collected the data
21 TB analyzed the data and designed the figures
22 ND and GMB interpreted the data
23 TB and AJ wrote the first version of the manuscript
24 CCW, IA, OR, JG, VM, JMM, CC, PT, BT, AR, JG helped to write the manuscript
25 ND and GMD wrote the final version of the manuscript
26 ND and GMB contributed equally
27 TB and AJ contributed equally

28
29 **Declaration of interests**

30 Prof Jean Michel Molina reports grants from Gilead, Merck and ViiV Healthcare, outside the
31 submitted work
32 Prof. Jade Ghosn reports grants and personal fees from Gilead, grants and personal fees from
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37 outside the submitted work

1 **Data sharing**

2 De-identified participant data and data dictionary are available upon reasonable request at
3 Prof Nicolas Dupin (Contact: nicolas.dupin@aphp.fr) and Prof Guillaume Martin-Blondel
4 (Contact: martin-blondel.g@chu-toulouse.fr)

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1 **Table 1** Characteristics of patients according to treatment regimen

| | Ceftriaxone (n=42) | Benzylpenicillin (n=166) | P-value* |
|---|-----------------------|-----------------------------|----------|
| Age (mean ± SD) | 44.4 ± 13.4 | 47.1 ± 12.2 | 0.23 |
| Male | 40 (95) | 153 (92) | 0.74 |
| PLWHA | 23 (55) | 79 (48) | 0.49 |
| History of syphilis | 1 (2) | 18 (11) | 0.13 |
| Neurosyphilis subtype (%) | | | 0.006 |
| Uveitis | 14 (33) | 90 (55) | |
| Anterior uveitis | 9 (21) | 50 (30) | |
| Intermediate uveitis | 8 (19) | 45 (27) | |
| Posterior uveitis | 11 (26) | 77 (47) | |
| with retinitis | 7 (17) | 53 (32) | |
| with papillitis | 8 (19) | 42 (25) | |
| Optic neuritis | 6 (14) | 3 (2) | |
| Meningitis | 8 (20) | 33 (20) | |
| Facial palsy | 1 (3) | 9 (5) | |
| Neurovascular | 4 (10) | 7 (4) | |
| Otic syphilis | 8 (19) | 41 (25) | |
| Other neurological signs (%) | | | 0.46 |
| Confusion | 2 (5) | 9 (5) | |
| Peripheral neuropathy | 3 (7) | 6 (4) | |
| Ataxia | 1 (2) | 3 (2) | |
| Myelitis | 1 (2) | 0 (0) | |
| Epilepsy | 0 (0) | 3 (2) | |
| Other clinical signs (%) | | | 0.36 |
| Eruption | 11 (26) | 49 (30) | |
| Lymphadenopathy | 2 (5) | 5 (3) | |
| Eruption and lymphadenopathy | 1 (2) | 13 (8) | |
| Alopecia | 1 (2) | 2 (1) | |
| Serum VDRL | 32 (16-128) | 64 (32-128) | 0.49 |
| CSF leucocytosis (elements/mm ³) | 42 ± 101 (n=38) | 53 ± 115 (n=128) | 0.57 |
| CSF proteins (mg/L) | 0.68 ± 0.40 (n=34) | 0.82 ± 0.68 (n=120) | 0.25 |
| Positive CSF VDRL | 8 (28) (n=29) | 55 (42) (n=114) | 0.05 |
| Treatment with systemic corticoids | 5 (12) | 48 (29) | 0.03 |

2 Quantitative variables are presented as the mean ± standard deviation and qualitative variables are presented as
3 the absolute value (%). Serum VDRL is presented as the median (IQR)

4 *All tests were two-tailed and considered significant if P-value<0.05. Fisher's exact tests or Student's t tests
5 were performed, as appropriate.

6 CSF: cerebrospinal fluid, PLWHA: People living with HIV/AIDS

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1 **Table 2** Endpoints according to treatment regimen

| | Ceftriaxone | Benzylpenicillin | P-value |
|--|------------------|------------------|---------|
| Complete response Propensity score- weighted OR* | 1.08 [0.94-1.24] | Ref | 0.269 |
| Overall response, Propensity score- weighted OR* | 1.22 [1.12-1.33] | Ref | <0.0001 |
| Length of hospital stay (days) [95% CI] | 8.9 [5.7-12.0] | 13.8 [12.8-14.8] | <0.0001 |
| Serological response Crude OR (<i>n</i> =117) | 1.56 [0.42-5.86] | Ref | 0.50 |
| Per protocol analysis | | | |
| Complete response Propensity score- weighted OR* | 1.22 [1.06-1.42] | Ref | 0.008 |
| Overall response Propensity score- weighted OR | 1.22 [1.11-1.34] | Ref | <0.0001 |
| Including CSF-VDRL (<i>n</i> =144) | | | |
| Complete response Propensity score- weighted OR* | 1.18 [1.01-1.38] | Ref | 0.04 |
| Overall response Propensity score- weighted OR | 1.27 [1.13-1.42] | Ref | <0.0001 |

2 *The variables included in the propensity score were age, sex, centre, HIV status, neurosyphilis subtype and
3 history of syphilis. OR: odds ratio
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1 **Figure 1** Diagram of included patients

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3 GP/TB: General paresis/ Tabes dorsalis
4 NS: Neurosyphilis
5 CSF: cerebrospinal fluid

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7 **Figure 2** Complete response rates in patients treated with ceftriaxone or benzylpenicillin, by
8 HIV status, subtype of neurosyphilis and CSF cellularity.

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11 HIV +: presence of human immunodeficiency virus infection
12 HIV -: absence of human immunodeficiency virus infection
13 CSF cells > 5/mm³: presence of more than 5 cells per mm³ in the cerebrospinal fluid.
14 CSF cells < 5/mm³: Presence of fewer than 5 cells per mm³ in the cerebrospinal fluid
15 OR: odds ratio
16 Odd Ratios and their confidence intervals are presented with a log-linear scale.
17 Vasculitis and facial palsy were grouped with meningitis because there were too few events.

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22 **Research in context**

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24 **Evidence before this study**

25 Neurosyphilis is a disease which, although rare, can have very serious consequences.
26 According to the European, US and UK guidelines, the gold-standard treatment is intravenous
27 benzylpenicillin for 10 to 14 days. Nonetheless, the same guidelines are not in line concerning
28 the use of ceftriaxone which could allow outpatient parenteral antimicrobial therapy and thus
29 reduce the duration of hospitalization.

30 In order to assess the evidence about ceftriaxone efficacy in treating neurosyphilis, we
31 searched Pubmed until June 1st 2020 entering the terms “neurosyphilis” AND “treatment”
32 with language restriction in English and French. Evidence-based-medicine remains scarce
33 about the effectiveness of ceftriaxone since only case reports and small studies were
34 published. Some studies were restricted to patients living with HIV, and to patients with
35 syphilitic uveitis, reporting a 80% and 67% response rate respectively.

36 To better assess the effectiveness of ceftriaxone among overall neurosyphilis, we performed
37 this multicentre, retrospective, observational study.

38
39 **Added value**

40 The aim of our study was to ascertain whether ceftriaxone could achieve the same clinical
41 outcomes than benzylpenicillin. Two groups of patients were defined on the basis of initial
42 treatment used to treat neurosyphilis: intravenous ceftriaxone (2 g once daily) or intravenous

1 benzylpenicillin (3-4 million units every four hours). We used an inverse probability
2 treatment weighting to address the indication bias. We found that, compared to
3 benzylpenicillin, ceftriaxone exhibited a weighted Odd Ratio of 1.22 [1.12-1.34] for clinical
4 overall response and 1.08 [0.94-1.24] for clinical complete response. Both groups did not
5 differ according to serological response, but hospital stay was shorter for the ceftriaxone
6 group. To our knowledge, this is the first large-scale multicentre study assessing the
7 effectiveness of ceftriaxone in neurosyphilis.

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9 **Implications of all the available evidence**

10 Our results suggest that ceftriaxone could represent a reliable alternative to benzylpenicillin to
11 treat neurosyphilis. Ceftriaxone may represent the first line treatment of neurosyphilis in
12 patients allergic to penicillin. Second, for selected patients ready for home discharges,
13 ceftriaxone used as outpatient parenteral antimicrobial therapy would reduce the duration of
14 hospitalization with costs savings and potential improvement of patients' quality of life.

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CIM-10
1998-2018

Patients hospitalized
with a coded
diagnosis of NS
(A521, A523, A504)
n= 365

Excluded patients n=157

Asymptomatic NS n= 37
Lack of data n= 41
Other diagnosis n=59
GP/TB n=6
Other treatment n=3
No CSF pleiocytosis n=11

Included patients
n=208

Initially treated with
benzylpenicillin
n=166

Initially treated with
ceftriaxone
n=42

| Subgroup | Ceftriaxone | Benzylpenicillin | OR |
|-------------------------------|--------------------|-------------------------|--------------------|
| Overall | 22/42 | 54/165 | 2.26 (1.14–4.49) |
| HIV + | 14/23 | 32/79 | 2.28 (0.89–6.09) |
| HIV – | 8/19 | 23/87 | 2.02 (0.71–5.64) |
| Uveitis | 8/14 | 28/90 | 2.95 (0.94–9.74) |
| Otic syphilis | 5/8 | 9/41 | 5.92 (1.18–29.67) |
| Neurosyphilis* | 8/13 | 21/46 | 1.90 (0.54–6.70) |
| CSF cells > 5/mm ³ | 14/23 | 38/102 | 2.14 (0.89–5.20) |
| CSF cells < 5/mm ³ | 6/13 | 2/27 | 10.71 (1.75–65.23) |

