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[Intervention Review]

Antibiotic therapy for adults with neurosyphilis

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ABSTRACT

Background

Neurosyphilis is an infection of the central nervous system, caused by *Treponema pallidum*, a spirochete capable of infecting almost any organ or tissue in the body causing neurological complications due to the infection. This disease is a tertiary manifestation of syphilis. The first-line treatment for neurosyphilis is aqueous crystalline penicillin. However, in cases such as penicillin allergy, other regimes of antibiotic therapy can be used.

Objectives

To assess the clinical effectiveness and safety of antibiotic therapy for adults with neurosyphilis.

Search methods

We searched the Cochrane Library, CENTRAL, MEDLINE, Embase, LILACS, World Health Organization International Clinical Trials Registry Platform and OpenGrey up to April 2019. We also searched proceedings of eight congresses to a maximum of 10 years, and we contacted trial authors for additional information.

Selection criteria

We included randomised clinical trials that included men and women, regardless of age, with definitive diagnoses of neurosyphilis, including HIV-seropositive patients. We compared any antibiotic regime (concentration, dose, frequency, duration), compared to any other antibiotic regime for the treatment for neurosyphilis in adults.

Data collection and analysis

Two review authors independently selected eligible trials, extracted data, and evaluated risk of bias. We resolved disagreements by involving a third review author. For dichotomous data (serological cure, clinical cure, adverse events), we presented results as summary risk ratios (RR) with 95% confidence intervals (CI). We assessed the quality of evidence using the GRADE approach.

Main results

We identified one trial, with 36 participants diagnosed with syphilis and HIV. The participants were mainly men, with a median age of 34 years. This trial, funded by a pharmaceutical company, compared ceftriaxone in 18 participants (2 g daily for 10 days), with penicillin G, also

in 18 participants (4 million/Units (MU)/intravenous (IV) every 4 hours for 10 days). The trial reported incomplete and inconclusive results. Three of 18 (16%) participants receiving ceftriaxone versus 2 of 18 (11%) receiving penicillin G achieved serological cure (RR 1.50; 95% CI: 0.28 to 7.93; 1 trial, 36 participants very low-quality evidence); and 8 of 18 (44%) participants receiving ceftriaxone versus 2 of 18 (18%) participants receiving penicillin G achieved clinical cure (RR 4.00; 95% CI: 0.98 to 16.30; 1 trial, 36 participants very low-quality evidence). Although more participants who received ceftriaxone achieved serological and clinical cure compared to those who received penicillin G, the evidence from this trial was insufficient to determine whether there was a difference between treatment with ceftriaxone or penicillin G.

In this trial, the authors reported what would usually be adverse events as symptoms and signs in the follow-up of participants. Furthermore, this trial did not evaluate recurrence of neurosyphilis, time to recovery nor quality of life. We judged risk of bias in this clinical trial to be unclear for random sequence generation, allocation, and blinding of participants, and high for incomplete outcome data, potential conflicts of interest (funding bias), and other bias, due to the lack of a sample size calculation. We rated the quality of evidence as very low.

Authors' conclusions

Due to low quality and insufficient evidence, it was not possible to determine whether there was a difference between treatment with ceftriaxone or Penicillin G. Also, the benefits to people without HIV and neurosyphilis are unknown, as is the ceftriaxone safety profile. Therefore, these results should be interpreted with caution. This conclusion does not mean that antibiotics should not be used for treating this clinical entity. This Cochrane Review has identified the need of adequately powered trials, which should be planned according to Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) recommendations, conducted and reported as recommended by the CONSORT statement. Furthermore, the outcomes should be based on patients' perspectives taking into account Patient-Centered Outcomes Research Institute (PCORI) recommendations.

PLAIN LANGUAGE SUMMARY

Antibiotic therapy for adults with neurosyphilis

Review Question

We reviewed the clinical effectiveness and safety of antibiotic therapy for adults with neurosyphilis.

Background

Syphilis is a condition caused by a micro-organism called *Treponema pallidum*. At any stage of syphilis an individual can acquire neurosyphilis, which is an infection of the central nervous system (brain and spinal cord). The infection can be spread throughout the central nervous system, causing complications in the brain and spine. It may occur during early or late syphilis and it can have severe consequences for patients. Research has shown that people who are also infected with HIV are more likely to get neurosyphilis. Antibiotics are used to treat neurosyphilis. The first option is aqueous crystalline penicillin. However, in some cases, such as penicillin allergy, other antibiotics can be used.

Study characteristics

We searched the medical literature up to April 2019 for trials that evaluated the effectiveness and safety of drugs proposed for the management of neurosyphilis in adults. We found only one randomised clinical trial that met our criteria (patients are randomly put into groups to receive different treatments). This trial involved 36 adults with both syphilis and HIV, who were mainly men, with a median age of 34 years. The trial compared two drugs: ceftriaxone (2 g once daily), and penicillin G (4 million units every 4 hours for 10 days). It was funded by a pharmaceutical company.

Key findings

The trial reported serological cure, which is a decrease in the levels of the infection shown by laboratory analysis of fluids in the brain and spinal cord (known as cerebrospinal fluids), and clinical cure, which is the absence of signs or symptoms of neurosyphilis. Only three of 18 participants receiving ceftriaxone and two of 18 participants receiving penicillin G achieved serological cure; and eight of 18 participants receiving ceftriaxone and two of 18 participants receiving penicillin G achieved clinical cure.

There was not enough evidence to allow us to state if there is a difference between treatment with ceftriaxone or Penicillin G for neurosyphilis in adults. The outcomes evaluated could change when trials with a better design become available. Additionally, we did not identify any evidence related to the effectiveness and safety of other drugs proposed to manage this condition.

Quality of evidence

The quality of the evidence was very low for the outcomes serological cure and clinical cure due to problems with the trial's design and methods, and because there was only a small number of participants.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Ceftriaxone compared to penicillin G for neurosyphilis

Ceftriaxone compared to penicillin G for neurosyphilis

Patient or population: people with neurosyphilis

Setting: hospital

Intervention: ceftriaxone

Comparison: penicillin G

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Nº of partici- pants (trials)	Quality of the evidence (GRADE)	Comments
	Risk with peni- cillin G	Risk with cef- triaxone				
Serological cure assessed by decrease in the CSF VDRL titre Follow-up: range 14 weeks-52 weeks	111 per 1000	167 per 1000 (31 to 881)	1.50 (0.28 to 7.93)	36 (1 RCT)	⊕⊕⊕⊕ Very low ^{1,2,3,4}	Analysis performed by ITT analysis. Trial only reported CSF decrease in 2 of 7 participants receiving ceftriaxone and 2 of 7 receiving penicillin
Clinical cure assessed by RPR decrease Follow-up: range 14 weeks-52 weeks	111 per 1000	444 per 1000 (109 to 1811)	4.00 (0.98 to 16.30)	36 (1 RCT)	⊕⊕⊕⊕ Very low ^{1,3,4}	Analysis performed by ITT analysis. Trial reported improvement in RPR titres in 8 of 10 participants receiving ceftriaxone and 2 of 15 receiving penicillin
Adverse events Any untoward medical oc- currence regarding medica- tions follow-up: range 1 week-52 weeks	0 per 1000	0 per 1000 (0 to 0)	Not estimable	(1 RCT)	⊕⊕⊕⊕ Very low ^{1,3,4,5}	Trial evaluated symptoms and signs in the included participants, but these were clinical characteristics of participants, and not defined as adverse events
Recurrence of neu- rosyphilis	0 per 1000	0 per 1000 (0 to 0)	Not estimable	(studies)	-	Trial did not assess this outcome
Time to recovery	0 per 1000	0 per 1000 (0 to 0)	Not estimable	(studies)	-	Trial did not assess this outcome
Quality of life	0 per 1000	0 per 1000 (0 to 0)	Not estimable	(studies)	-	Trial did not assess this outcome

Withdrawals	111 per 1000	222 per 1000 (47 to 1000)	RR 2.00 (0.42 to 9.48)	36 (1 RCT)	⊕⊕⊕⊕ Very low ^{1,3}
Follow-up: range 1 week-52 weeks					

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI)

CI: Confidence interval; **CSF:** cerebrospinal fluid; **ITT:** intention-to-treat; **RPR:** rapid plasma reagin; **RR:** Risk ratio; **VDRL:** Venereal Disease Research Laboratory

GRADE Working Group grades of evidence

High quality: we are very confident that the true effect lies close to that of the estimate of the effect.

Moderate quality: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low quality: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.

Very low quality: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

¹Downgraded two levels due to limitations in the trial design and execution of trials.

²Downgraded two levels due to few events and incomplete data regarding outcome, 95% confidence interval was between 0.28 and 7.93.

³Not all the participants received the exact same tests to determine microbiological and clinical cure. Also, the sample size was very small and there was a very low number of events, which had an impact on the precision of the effect estimates.

⁴Downgraded two levels due to the small sample size and very low number of events, which had an impact on the precision of the effect estimates

⁵Downgraded two levels due to few events and incomplete data regarding outcome, 95% confidence interval was between 0.98 and 16.30.

BACKGROUND

Description of the condition

Neurosyphilis is a tertiary manifestation of syphilis, an infection of the central nervous system (CNS) caused by *Treponema pallidum* (Anonymous 2017; Hook 2017). It is a spirochete capable of infecting almost any organ or tissue in the body causing protean clinical manifestations (Conde-Sendín 2002; Philip 2014). The spirochete can be disseminated systemically causing neurological complications. It may occur during early or late syphilis (Berger 2014). There are two forms of neurosyphilis: an early form that usually affects the cerebrospinal fluid (CSF), meninges, and vasculature, and the late form, which affects the brain and spinal cord parenchyma (Rowland 2010). In many cases it goes unnoticed although approximately one-third of people infected with *T pallidum* display CSF abnormalities, such as pleocytosis, elevated protein concentration or reactivity for serological test, suggestive of CNS invasion by *T pallidum*. Between 1% and 5% of people with neurosyphilis develop neurological symptoms (Berger 2014; Marra 2009; O'Donnell 2005).

The epidemiology of neurosyphilis has largely paralleled that of syphilis in general (Berger 2014; Unemo 2017). By the early 1950s, a dramatic decline occurred as a consequence of the widespread use of antibiotics (Berger 2014). However, incidence has increased due to the onset of the AIDS pandemic (Chen 2017; Kent 2008; Van der Bij 2005). Currently, early neurosyphilis is more common than late neurosyphilis, and it is most frequently seen in people with HIV infection (Van der Bij 2005). Worldwide, it was estimated that by 1999, 11.6 million new cases of syphilitic infection were occurring per year (Berger 2014). In 1999, there were approximately 107,000 new cases in North America, 136,000 new cases in Western Europe, 3.8 million new cases in Sub-Saharan Africa, 4 million cases in South Asia, and 2.9 million cases in Latin America (Berger 2014). A study conducted in the Netherlands showed an incidence of neurosyphilis of 0.47 per 10,000 adults, about 60 new cases per year, and suggests that, given the frequency of atypical manifestations of the disease, reintroduction of screening for neurosyphilis has to be considered (Daey 2014).

Among clinical symptoms, the earliest manifestation of neurosyphilis is syphilitic meningitis, which typically occurs within the first 12 months of infection. The symptoms of syphilitic meningitis are headache, photophobia and stiff neck (Berger 2014). Acute meningeal syphilis can occur early in syphilis infection and is a well-described feature of secondary syphilis; hearing loss, tinnitus, and vertigo are symptoms that can be observed in 40% of people with secondary syphilis (Berger 2014). Late neurological complications of syphilis, which present after long periods of latency, are caused by meningovascular, or parenchymal damage, or both. Vascular involvement leading to focal ischemia can present with neurological deficits, including hemiparesis, aphasia, and focal or generalised seizures (Cohen 2013). General paresis is a chronic meningoencephalitis, with direct invasion of the cerebrum by *T pallidum*, which usually manifests after 15 to 20 years, and includes manifestations of progressive dementia with changes in personality, affect, sensorium, intellect, and speech (Cohen 2013). The characteristics of neurosyphilis may be modified by the concomitant presence of immunosuppressive agents or conditions such as HIV/AIDS (Zetola 2007). HIV infection may be associated with an increased risk of development of early neurological complications, likely due to the inability to control

the CNS infection after invasion (Zetola 2007). See Appendix 1 for medical terms.

Diagnosis of neurosyphilis is based on serological tests that are divided into two categories: non-treponemal and treponemal tests. All non-treponemal tests measure immunoglobulin (Ig) G and IgM antiphospholipid, and all treponemal tests use *T pallidum* or its components as the antigen if lesion exudate or tissue are available (Ratnam 2005). The treponemal tests usually used for diagnosis of neurosyphilis are fluorescent treponemal antibody absorption test (FTA ABS) and serum microhemagglutination-*T pallidum* (MHA-TP). Non-treponemal tests used are plasma reagin (RPR), or Venereal Disease Research Laboratory (VDRL) (Berger 2014). See Appendix 2 for details of the operative performance of each test.

Additionally, the diagnosis of neurosyphilis in patients with clinical manifestations of neurosyphilis uses CSF findings supported by other laboratory tests, such as positive VDRL or positive CSF FTA-ABS, and white blood cell count (polymorphonuclear leucocytes and/or lymphocytes) greater than 5 m/μL or CSF protein greater than 0.45 g/μL or IgG Index greater than 0.6 (Timmermans 2004). On the other hand, CSF should be examined in any patient with syphilis and any neurological or ophthalmic symptoms or signs (cognitive dysfunction, motor or sensory defects, visual or auditory symptoms, cranial nerve palsies, meningismus, etc.). A CSF examination should also be considered in patients who fail to respond to therapy with an appropriate decline in nontreponemal antibody titre (Katz 2012). See Appendix 3 for details of the criteria for neurosyphilis diagnosis.

Four antibiotic groups are prescribed in adults with neurosyphilis: β-lactam antibiotics, tetracyclines, macrolides. Additionally, chloramphenicol is used to treat the disease (Berger 2014; Conde-Sendín 2002).

Description of the intervention

β-lactam antibiotics

Since 1940, intramuscular penicillin G has been demonstrated to be clearly beneficial for serological and clinical cure for neurosyphilis (Mahoney 1984; Ghanem 2010). It is the first-line option drug for treating people at any stage of syphilis, and remains as an effective first-line treatment (Berger 2014). The choice of preparation (i.e. benzathine, aqueous procaine, or aqueous crystalline), its dosage and the treatment duration are determined by the stage and manifestations of the disease (Berger 2014). According to international guidelines for treating neurosyphilis, crystalline penicillin should be administered in doses of 24 million units intravenous from 10 to 14 days (Archer 2011; CDC 2015; French 2009). Procaine penicillin should be administered in doses of 2.4 million units intramuscular once daily plus probenecid 500 mg orally four times a day, both for 10 to 14 days. Some specialists administer benzathine penicillin but studies revealed that the drug levels in the CSF are too low to eliminate *T pallidum* (Mohr 1976; Musher 2008).

This antimicrobial group is the most frequent elicitor of drug hypersensitivity reactions (Chambers 2001; Torres 2010). However, β-lactams are generally safe drugs; serious adverse events are rare, and allergy is over-diagnosed. In fact, severe hypersensitivity reactions to benzathine penicillin are scarce, with an estimated incidence of three cases of anaphylaxis per 100,000 treated

(Galvao 2013; Lagacé-Wiens 2012; Pietri 2001). There is a particular reaction in people with syphilis when they receive antibiotic, namely the Jarisch-Herxheimer reaction. It is a transient immunological reaction, characterised by symptoms such as fever, chills, headache, myalgia, and exacerbation of existing cutaneous lesions. These clinical findings are manifested over a short-term period, that is, 24 hours after starting treatment (Belum 2013).

Ceftriaxone, a third-generation cephalosporin, is another β -lactam antibiotic used for treating people with neurosyphilis. It is active in vitro against *T pallidum* with a good blood-brain barrier penetration. Ceftriaxone should be administered in doses of 2 g daily intravenous or intramuscular for 10 to 14 days. It is considered as an alternative for neurosyphilis patients with penicillin allergy, when penicillin anaphylaxis is considered an absolute contraindication (Pietri 2001). Cross-reactivity between penicillins and cephalosporins are overstated, indeed, the risk with third- and fourth-generation cephalosporin is negligible (Pichichero 2007).

Tetracyclines

Tetracyclines are active against *T pallidum* (Deck 2012). Doxycycline is considered an alternative regime for neurosyphilis treatment and can be used at 100 mg orally, twice a day, for 21 to 30 days. This drug is a second-generation tetracycline with increased oral bioavailability and tissue penetration. Doxycycline is absorbed in the duodenum and effective concentrations may be achieved in the CSF in patients with neurological infections. Another option is tetracycline 500 mg orally, four times daily, for 30 days (Yim 1985). The most common side effects are pill oesophagitis, photosensitivity, and staining of teeth and bone (Eisen 2010).

Macrolides

Erythromycin is active against *T pallidum* (Deck 2012). The recommended erythromycin regime for people with neurosyphilis is 500 mg orally, four times a day, for 30 days (Berger 2014). The most frequent adverse events associated with this drug are anorexia, nausea, vomiting, diarrhoea, and gastrointestinal intolerance, which are due to a direct stimulation of intestinal motility, and are a common reason for discontinuing erythromycin and substituting with another antibiotic. Erythromycins can produce acute cholestatic hepatitis (fever, jaundice, impaired liver function), probably as a hypersensitivity reaction. Other allergic reactions include fever, eosinophilia, and rashes (Deck 2012).

Chloramphenicol

Chloramphenicol has been used to treat neurosyphilis as an additional treatment option: 1 g endovenously for 14 days (Ambrose 1984; Conde-Sendín 2002). However, it can cause disturbances in red cell maturation and irreversible aplastic anaemia (Guglielmo 2014). Due to the above, chloramphenicol is no longer available; it was withdrawn after a Food and Drug Administration (FDA) recommendation (FDA 2012).

How the intervention might work

The aim of neurosyphilis treatment is to obtain sufficiently high antibiotic levels in the CNS during the long and irregular time frame where the bacteria is reproducing. Therefore, the treatment should be long and antibiotic-dose high (Conde-Sendín 2002).

The β -lactam antibiotics share a common structure and mechanism of action: inhibition of synthesis of the bacterial peptidoglycan cell wall, which is essential for their normal growth and development (Pietri 2001). They inhibit the growth of sensitive bacteria by inactivating enzymes located in the bacterial cell membrane, called penicillin binding proteins (PBPs). Therapeutic concentrations of penicillins are achieved readily in tissues and in secretions such as joint fluid, pleural fluid, pericardial fluid, and bile. CSF penetration is poor except in the presence of inflammation. Penicillin concentration in the CSF is variable but it is less than 1% plasma when the meninges are normal (Pietri 2001). When there is inflammation, concentrations in CSF may increase to as high as 5% of the plasma value. Penicillins are eliminated rapidly, particularly by glomerular filtration and renal tubular secretion, such that their half-lives in the body are short, typically 30 to 90 minutes, and require frequent administration when given parenterally. Probenecid blocks the renal tubular secretion of penicillin. Therefore, the concurrent administration of probenecid prolongs the elimination of penicillin G and, consequently, increases the serum concentrations. As a consequence, concentrations of these drugs in urine are high (MacDougall 2011).

Among tetracyclines, doxycycline has the longest experience for the treatment of CNS infections. The lipophilic drug doxycycline is readily absorbed (> 80%) after oral application (Nau 2010). Tetracyclines are bacteriostatic antibiotics that inhibit protein synthesis by binding reversibly to 16S rRNA of the 30S ribosomal subunit (Stamm 2010); tetracyclines have a 30% excretion through urine and faeces to 20% to 60% (Agwuh 2006). On the other hand, erythromycin belongs to the macrolides group, antibiotics that are protein-synthesis inhibitors; specifically, they block the peptidyl transferase region in domain V of 23S rRNA (Stamm 2010). Macrolides penetrate well into tissue, but because of their relatively high molecular mass, and probably also because of their affinity for P-glycoprotein, they do not reach sufficient CSF concentrations in the absence of meningeal inflammation. The excretion of erythromycin is mainly through faeces followed by urine: 2% to 5% as an unchanged molecule (Nau 2010; Thompson 1980). These groups of antibiotics inhibit the protein synthesis of *T pallidum* and interfere with protein synthesis in protein in human cells (Levinson 2012).

Why it is important to do this review

Since 2000, incidence of early-stage syphilis in the USA and Europe has increased (Marra 2004). Adequate treatment for people with neurosyphilis is fundamental for prevention of neurological sequelae. According to international guidelines, aqueous crystalline penicillin is the first-line treatment for neurosyphilis, while procaine penicillin plus probenecid, amoxicillin, ceftriaxone, and doxycycline could be used as alternative regimes when parenteral administration is not feasible (CDC 2015; French 2009). Current recommendations are based on what is known about the pharmacokinetics of the available drugs, the effect on *T pallidum* in vitro, laboratory considerations, biological plausibility, expert opinion, case studies, and clinical experience (CDC 2015). However, *T pallidum* is highly sensitive to penicillin, and *T pallidum* is capable of acquiring plasmids that produce the enzyme penicillinase. Clinical data are lacking on the optimal dose and duration of treatment and the long-term efficacy of antimicrobials other than penicillin (CDC 2015; Kingston 2008). The safety profile

in the treatment for neurosyphilis could bring many potential complications. Jarsich-Herxheimer is one, but other adverse reactions are also associated with antibiotic administration (Ali 2002; Chen 2017). In this scenario it is important to demonstrate what potential complications are associated with the treatment for neurosyphilis.

When patients are immunocompromised, that is, patients with HIV infection, they have a higher likelihood of developing neurosyphilis (Berger 2014). Penicillin remains the first choice of treatment for neurosyphilis, and research has shown that infectious disease specialists often treat secondary syphilis among HIV-infected patients with three doses of benzathine penicillin G instead of one dose of penicillin, leading to a high probability of adverse effects, including allergic reaction, neurotoxicity, and neutropenia, among others (Jinno 2013). Additionally, the CDC guideline states that patients with HIV might have higher rates of serological treatment failure with recommended regimens compared to those without HIV (CDC 2015). Due to the above, it was necessary to know the clinical effectiveness of different therapies as an option to treat patients with neurosyphilis, and at the same time, there is a need to conduct a critical appraisal of the randomised clinical trials in this subgroup of patients (Lasso 2009).

OBJECTIVES

To assess the clinical effectiveness and safety of antibiotic therapy for adults with neurosyphilis.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomised clinical trials with parallel design. We excluded quasi-randomised trials because this type of study could bring effect estimates that indicate more extreme benefits when they are compared with randomised clinical trials (O'Connor 2011).

Types of participants

Men and women, regardless of age. We included people with a definitive diagnosis of neurosyphilis and, due to the absence of consensus on diagnostic criteria for neurosyphilis and HIV, and the complications of interpretation of CSF abnormalities when a HIV coinfection is present, we also included people who had a definitive diagnosis of neurosyphilis and who were also HIV-seropositive (Berger 2014). We adopted the recommendations for diagnosis of neurosyphilis in the phase of HIV infection detailed by Berger 2014 (see Appendix 3 for details).

Types of interventions

Penicillin (any concentration, presentation frequency and duration), compared to any other antibiotic regime.

Types of outcome measures

Primary outcomes

- Serological cure: defined as a decrease in the CSF Venereal Disease Research Laboratory test (VDRL) titre by two dilutions or reversion to non-reactive within two years after completion of therapy for patients with definitive diagnosis of syphilis (Ali 2002; Nayak 2012). The CSF should be examined at the end of

treatment to document a fall in cell count, and it should then be examined at six-month intervals for two to three years. The leukocyte count should return to normal within one year of treatment (usually six months), and the protein level should return to normal within two years (Berger 2014).

- Clinical cure: defined as continued absence of signs or symptoms, or the serum RPR decreasing by four-fold within two years of treatment (Bilgrami 2014)
- Adverse events: in general defined by the International Conference on Harmonisation (ICH) Guidelines for Good Clinical Practice (ICH-GCP 1997), as any untoward medical occurrence that at any dose results in death, is life-threatening, requires inpatient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or is a congenital anomaly or birth defect. We considered all other adverse events as non-serious (ICH-GCP 1997). Within adverse events, we planned to describe reported outcomes, such as the Jarisch-Herxheimer reaction, a common manifestation that is a transient immunological reaction characterised by constitutional symptoms such as fever, chills, headache, myalgias, and exacerbation of existing cutaneous lesions after the administration of β -lactam antibiotics (Belum 2013). Also, we planned to describe other adverse events related to other antibiotic regimes administered, such as pill oesophagitis, photosensitivity, staining of teeth and bone in tetracycline administration, or fever, eosinophilia, and rashes in macrolides.

Secondary outcomes

- Recurrence of neurosyphilis: recurrent or persistent symptoms or a sustained four-fold increase in non-treponemal test titres despite appropriate treatment (Brown 2003)
- Time to recovery: defined as the time to achieve clinical or serological cure
- Quality of life, according to the definition of the concept adopted in each trial and using any validated scale
- All causes of withdrawals: defined as any retirement of an individual in a trial

Search methods for identification of studies

We used electronic searching in bibliographic databases and handsearching, as described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Lefebvre 2011). We downloaded and managed the search results using the EndNote bibliographic software.

Electronic searches

We performed the search in collaboration with the Cochrane Sexually Transmitted Infections' (STI) Information Specialist and a healthcare librarian. We used a combination of exploded controlled vocabulary (MeSH, Emtree, DeCS), and free-text terms (considering spelling variants, plurals, synonyms, acronyms, and abbreviations), for 'neurosyphilis' and 'antibiotic therapy', with field labels, truncation, proximity operators, and Boolean operators (see Appendix 4 for search strategies).

We searched the following databases up to April 2019:

- the STI Specialised Register of trials;

- the Cochrane Central Register of Controlled Trials (CENTRAL; 2019, Issue 4), via OVID;
- Ovid MEDLINE (1946 to April 2019);
- Embase Elsevier (1974 to April 2019);
- LILACS via iAHx interface (1982 to April 2019).

We did not apply any restrictions on language or date.

We also searched the following clinical trials registries:

- World Health Organization International Clinical Trials Registry Platform (ICTRP; apps.who.int/trialsearch)
- ClinicalTrials.gov (clinicaltrials.gov)

We searched Open Grey (www.opengrey.eu) for grey literature.

Searching other resources

We handsearched conference proceeding abstracts of the following events:

- International Society for Sexually Transmitted Diseases Research (ISSTD; www.isstdr.org), 2007, 2009, 2011, 2013, 2015 and 2017;
- British Association for Sexual Health and HIV (BASHH; www.bashh.org), 2004, 2006, 2007, 2009, 2014, 2015, 2016, 2017 and 2018;
- International Congress on Infectious Diseases (ICID; www.isid.org), 2010 and 2012;
- International Union against Sexually Transmitted Infections (IUSTI; www.iusti.org), 2011 and 2012;

- International Society for Infectious Diseases (ISID; www.isid.org), 2011 and 2017;
- International Meeting on Emerging Diseases and Surveillance (IMED; www.isid.org), 2007, 2009 and 2011;
- Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC; www.asm.org), 2011 and 2012;
- International Federation of Gynecology and Obstetrics (FIGO; www.figo.org), 2015, 2018.

We screened the reference lists of all selected trials. We contacted the main authors to identify any additional published or unpublished data. Additionally we searched other sources with the terms 'neurosyphilis', 'neurolues' and 'tabes dorsalis'.

Data collection and analysis

Selection of studies

We followed the methods for study selection by using the steps recommended by the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011a). Two review authors (DB, LOC) independently screened the titles and abstracts to identify potential trials for inclusion eligibility, using Early Review Organizing Software (EROS; Ciapponi 2011; Glujovsky 2011; McQuay 1998). When the screening was not satisfactory, based on the title and abstract, we obtained the full-text article for assessment. We have presented the results of the trial selection as a PRISMA flowchart (Moher 2009; Figure 1). We resolved disagreements through discussion and consensus. A third review author (AMC) acted as referee when necessary. We contacted the trial authors to resolve doubts about available information or in case of disagreements.

Figure 1. Flow of information through the different phases of the review

Data extraction and management

Two review authors (DB, LOC) independently assessed for inclusion all the titles and abstracts of records retrieved from the search results. We resolved any disagreements through discussion or, if required, we consulted a third review author (AMC).

Data extraction format

We developed and piloted a standardised form to extract data. Two review authors (DB, LOC) independently extracted the following data from the included trials.

- Study location and setting
- Trial design and power calculation
- Ethical approval
- Inclusion and exclusion criteria
- Baseline characteristics of trial participants including sex, age, sexual orientation, pregnancy status for women, diagnostic test used to detect *T pallidum*

- Types of intervention: opportunistic or systematic invitation for screening; number of screening rounds, screening interval
- Types of comparison group: usual care, alternative screening method
- Types of outcome: primary, secondary
- Report of methodological characteristics (see [Assessment of risk of bias in included studies](#) for details)
- Number of people assessed for eligibility
- Numbers randomised to intervention and comparison groups
- Numbers receiving screening in intervention and comparison groups (at each screening round if multiple rounds)
- Numbers included in analyses in intervention and comparison groups
- Numbers with outcomes in intervention and comparison groups

One review author (DB) entered data into Review Manager 5 ([Review Manager 2014](#)), and two review authors (AJ, AMC)

independently checked for accuracy. When necessary, we also contacted the corresponding trial authors for further details.

Assessment of risk of bias in included studies

Two review authors (DB, LOC) independently assessed the risk of bias for each included study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2017). We resolved any discrepancies through discussion with AMC. Those assessing risk of bias are content and methodology experts. When we needed to obtain missing information, we contacted the trial authors using open-ended questions. We assessed risk of bias in the included trials and collected information in data extraction forms. We then added the information to Review Manager 5 (Review Manager 2014)

We assessed the following 'Risk of bias' domains, as set out in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2017).

- Random sequence generation
- Allocation concealment
- Blinding of participants, personnel
- Blinding of outcome assessment
- Incomplete outcome data
- Selective outcome reporting
- Other sources of bias

We also applied the criteria defined by Tramacerre 2015 for assessing the risk of bias. To summarise the quality of the evidence we considered allocation concealment, blinding of outcome assessor, and incomplete outcome data in order to classify each study as at: low risk of bias when we judged all of the three criteria as at low risk of bias; high risk of bias when we judged at least one criterion as at high risk of bias; unclear risk of bias when we judged all of the three criteria as at unclear risk of bias; and moderate risk of bias in the remaining cases. We assessed the overall risk of bias by outcome, taking into account the number the included studies with the outcome of interest and the sample size of the study. With reference to the first seven domains above, we assessed the likely magnitude and direction of the bias and whether we considered it was likely to affect the findings.

Measures of treatment effect

We expected to find dichotomous data regarding (serological cure, clinical cure, adverse events, recurrence of neurosyphilis, withdrawals). However, we only found results regarding serological cure, clinical cure, adverse events. We presented results as summary risk ratios (RR) with 95% confidence intervals (CIs). The RR as a relative effect measure has consistency, works well with a low or high rate of events, and is easy to interpret and use in clinical practice.

Unit of analysis issues

When we identified a clinical trial that randomly assigned participants into several intervention groups, we considered the control group to be the group that was receiving β -lactam antibiotic regime and the intervention group to be the group that was receiving other antibiotic schemes in the management of adults with neurosyphilis.

Dealing with missing data

In the case of missing data on participants or missing statistics (such as standard deviations), we contacted the trial authors.

Assessment of heterogeneity

We planned to assess statistical heterogeneity by graphical interpretation and with an I^2 statistic (Higgins 2003), and χ^2 test (Deeks 2017). We planned to judge heterogeneity as considerable if I^2 statistic was greater than 50% or if the P value in the χ^2 test was less than 0.10 (Deeks 2017). However, in the present review we only identified one trial (Marra 2000), and we could not assess heterogeneity.

Assessment of reporting biases

We planned to assess publication bias by using a funnel plot, which is usually used to illustrate variability between trials in a graphical way. We needed at least 10 trials in order to be able to make judgements about asymmetry and, if asymmetry were present, we would have attempted to explore other causes for it (Sterne 2011). However, in the present review we only identified one trial (Marra 2000), and we could not report biases.

Data synthesis

We planned to carry out statistical analyses using Review Manager 2014. We planned to use fixed-effect meta-analysis for combining data where it was reasonable to assume that trials were estimating the same underlying treatment effect. However, in the present review, we only identified one trial (Marra 2000), and we could not perform data analysis.

Trial sequential analysis

We planned to apply trial sequential analysis as cumulative meta-analyses are at risk of producing random errors due to sparse data and repetitive testing of the accumulating data (Brok 2009; Wetterslev 2008). To minimize random errors, we planned to calculate the required information size (i.e. the number of participants needed in a meta analysis to detect or reject a certain intervention effect) (Wetterslev 2008). We planned to perform a meta-analysis, and base the diversity-adjusted required information size on the event proportion in the control group; assumption of a plausible RR reduction of 20%. However, in the present review we only identified one trial (Marra 2000), and we could not perform a trial sequential analysis.

Subgroup analysis and investigation of heterogeneity

We planned to perform subgroup analysis for primary outcomes. If necessary, we planned to perform post hoc subgroup analyses. We planned to specify the reason sufficiently interpreted the results with caution. However in the present review we only identified one trial (Marra 2000), and we could not perform subgroup analysis.

Sensitivity analysis

If the searches identified sufficient trials, we planned to conduct sensitivity analyses as follows:

- including only randomised clinical trials at low risk of bias (Deeks 2017). As it was unlikely that we would find many trials at low risk of bias in all domains, we chose to focus on three core

domains, namely: generation of allocation sequence, allocation concealment, and blinding or masking;

- repeating the analysis taking attrition bias into consideration.

However, in the present review we only identified one trial ([Marra 2000](#)), and we could not perform sensitivity analysis by risk of bias.

Grading the quality of evidence

The GRADE approach specifies four levels of quality (high, moderate, low and very low), starting from high for randomised clinical trials. We planned to explore the impact of the level of bias by undertaking sensitivity analyses (see [Sensitivity analysis](#)), and we used the GRADE approach in order to produce a 'Summary of findings' table ([GRADEpro GDT 2015](#); [Schünemann 2017](#)). We downgraded the quality of evidence depending on the presence of the following factors:

- study limitations;
- inconsistency of results;
- indirectness of evidence;
- imprecision;
- publication bias.

RESULTS

Description of studies

See [Summary of findings for the main comparison](#).

Results of the search

We identified only one trial ([Marra 2000](#)). The search of electronic databases (CENTRAL, MEDLINE, Embase and LILACS) yielded 60 records and the search of other sources identified three records. After removing duplicates and reviewing the titles and abstracts, we discarded 34 citations. We reviewed the full text of 15 studies; 13 did not fulfil the criteria to be included in this systematic review so we excluded them, and one trial is awaiting classification. We contacted the authors of this trial but we could not retrieve the full-text article ([Serragui 1999](#)). See [Figure 1](#).

Included studies

We identified one multicenter, parallel-design trial, which involved 36 participants with syphilis and HIV-1 infection ([Marra 2000](#)). Ninety two percent of participants were male (33/36), with a median of age of 34 years. [Marra 2000](#) compared ceftriaxone (2 g,

intravenous (IV) once daily), or penicillin G (4 MU, IV, every 4 hours). Eighteen participants were randomised to receive ceftriaxone for 10 days and 18 participants were randomised to receive penicillin G for 10 days. The trial was conducted in the United States. . See [Characteristics of included studies](#) section for details. The outcomes evaluated regarding serological cure were CSF WBC counts, CSF protein concentrations and , regarding clinical cure serum RPR titers. In this clinical trial the authors reported what usually are adverse events as symptoms and signs in the follow-up of participants.

[Marra 2000](#) did not evaluate recurrence of neurosyphilis, time to recovery or quality of life.

[Marra 2000](#) was funded by the pharmaceutical industry, and was conducted between October 1991 through April 1994. However, the results were published in 2000.

Excluded studies

We excluded 14 studies: four were not clinical trials ([Hahn 1952](#); [Philcox 1987](#); [Starzycki 1990](#); [Dunaway 2017](#)), four were case series reports ([Goldman 1950](#); [Kopp 1949](#); [Orban 1957](#); [Tempski 1958](#)), two did not include participants with neurosyphilis ([Smith 2004](#); [Rolfs 1997](#)), three were narrative reviews ([Chesney 1949](#); [Clement 2014](#); [Short 1966](#)), and one included two participants with neurosyphilis but did not report any results outcomes regarding those two participants ([Pottthoff 2009](#)). See [Characteristics of excluded studies](#) section for details.

Studies awaiting classification

One trial is awaiting classification ([Serragui 1999](#)). We only had access to the trial abstract and it was not clear whether it was a clinical trial. We contacted the trial authors to get the full text and we have had no reply yet. See [Characteristics of studies awaiting classification](#) for details.

Ongoing trials

We did not find any ongoing trials regarding treatment for neurosyphilis in adults.

Risk of bias in included studies

We summarised the 'Risk of bias' assessment for [Marra 2000](#) in [Figure 2](#) and [Figure 3](#). We have also presented additional details of the trial in the [Characteristics of included studies](#) table.

Figure 2. 'Risk of bias' summary: review authors' judgements about each risk of bias item for each included study

Figure 3. 'Risk of bias' graph: review authors' judgements about each risk of bias item presented as percentages across all included studies

Random sequence generation

The trial authors reported [Marra 2000](#) as randomised, but it did not contain a description of the process of sequence generation, therefore, we considered it at unclear risk of bias.

Allocation

[Marra 2000](#) did not contain a description of the process of sequence generation, so we considered it at unclear risk of bias.

Blinding

We rated [Marra 2000](#) as being at unclear risk of bias for blinding because there was insufficient information about masking of participants and outcome evaluators to permit us to make a judgment of 'low risk' or 'high risk'.

Incomplete outcome data

[Marra 2000](#) initially randomised 36 participants but the trial authors reported an overall withdrawal of 17% (6/36). In the group receiving ceftriaxone, four of 18 participants were not included in the analysis, and in the group receiving penicillin G, two of 18 participants were not analysed. In both groups the participants were not included in the analysis due to loss to follow-up, so we considered this trial as having a high risk of attrition bias.

Selective reporting

The trial authors reported baseline characteristics for the 30 participants who received ceftriaxone or penicillin G for neurosyphilis treatment. However, the trial authors' report of the proportion of participants with improved CSF-VDRL RPR titres was imprecise regarding the period of time over which the tests took place. Also, the trial authors only reported results in CSF-VDR after treatment in seven participants who received ceftriaxone and in seven participants who received penicillin G. Regarding RPR titres, the trial authors only reported results after treatment in 10 participants receiving ceftriaxone and 15 participants receiving penicillin G. Therefore, we considered this trial to be at high risk of selective reporting bias.

Other potential sources of bias

The trial authors did not describe the procedure they used to calculate a sample size, which generated a design bias ([Porta 2014](#)). Additionally this study was funded by the pharmaceutical industry.

Effects of interventions

See: [Summary of findings for the main comparison Ceftriaxone compared to penicillin G for neurosyphilis](#)

Results are based on one study ([Marra 2000](#)). See [Summary of findings for the main comparison](#) for details of grading the quality of evidence.

Ceftriazone versus penicillin G

Primary outcomes

Serological cure

[Marra 2000](#), our single included trial, compared ceftriaxone with penicillin G and showed inconclusive effects regarding serological cure, with three of 18 participants (16%) in the ceftriaxone group versus two of 18 participants (11%) in the penicillin G group reporting serological cure (RR 1.50, 95% CI 0.28 to 7.93; 1 study, 36 participants, very low-quality evidence due to risk of bias, inconsistency and imprecision; [Analysis 1.1](#)). Although [Marra 2000](#) reported an intention-to-treat analysis in the methods section, the results regarding serological cure were reported only in seven participants who received ceftriaxone and seven participants who received penicillin G.

Clinical cure

[Marra 2000](#) found inconclusive evidence comparing ceftriaxone (8/18 (44%)), versus penicillin (2/18 (11%)), in terms of clinical cure (RR 4.00, 95% CI 0.98 to 16.30; 1 study, 36 participants, very low-quality evidence due to risk of bias, inconsistency and imprecision; [Analysis 1.2](#)). Although [Marra 2000](#) reported an intention-to-treat analysis in the methods section, the results regarding clinical cure were reported only in 10 participants who received ceftriaxone and 15 participants who received penicillin G.

Adverse events

In [Marra 2000](#), the trial authors reported symptoms and signs in the included participants as clinical characteristics. We did not consider them as adverse events, so, as a result, we considered that this trial did not report the measurement of adverse events as a primary outcome. We considered this as inappropriately reported adverse events.

Secondary outcomes

Recurrence of neurosyphilis

[Marra 2000](#) did not provide information about this outcome.

Time to recovery

[Marra 2000](#) did not provide information about this outcome.

Quality of life

[Marra 2000](#) did not provide information about this outcome.

All-cause withdrawals

There was no difference between the ceftriaxone group (4/18 (22%)), compared with the penicillin G group (2/18 (11%)), with respect to all-cause withdrawals (RR 2.00, 95% CI 0.42 to 9.58; very low quality evidence due to limitations in the trial design and execution of the trial, with an incomplete data report; [Marra 2000](#); [Analysis 1.3](#)).

DISCUSSION

Summary of main results

One trial met the inclusion criteria for this review ([Marra 2000](#)). The trial was conducted in the USA and its aim was to compare the responses of HIV-infected patients to treatment for neurosyphilis with endovenous ceftriaxone or endovenous penicillin. This trial compared ceftriaxone (2 g IV once daily for 10 days), versus penicillin G (4 MU IV every 4 hours for 10 days), as treatment for neurosyphilis. The study included 18 participants in each group; the trial authors were not specific regarding the randomisation method and blinding. Although they stated that the analysis was by intention-to-treat, they reported results regarding serological cure in seven participants from each group, and for clinical cure they reported data in 10 participants receiving ceftriaxone and in 15 participants receiving penicillin. Due to the above, we judged the risk of bias to be unclear in the domains of random sequence generation, allocation concealment, blinding of participants and blinding of outcome assessors; and as high risk in the domains of incomplete data, selective reporting and other biases. Although the proportion of participants who achieved clinical and serological cure was higher in the group that received ceftriaxone, due to incomplete evidence it was not possible to affirm that there is a difference between treatment with ceftriaxone or Penicillin G for neurosyphilis in adults. In addition to the limitations of the quality of the evidence, we cannot be sure about the differences between treatments. Also, the trial did not report adverse events appropriately. We rated the quality of the evidence as very low due to high risk of bias and imprecision issues.

Overall completeness and applicability of evidence

The review found inconclusive evidence to support or refute the use of ceftriaxone for treating people with neurosyphilis.

This conclusion is based on one very small trial with flawed methodology, conducted in participants with HIV infection complicated by neurosyphilis ([Marra 2000](#)). The trial authors themselves pointed out that there were severe differences between the two arms that limited the ability to make useful comparisons ([Marra 2000](#)). It has been pointed out that simple randomisation may not prevent bias in a smaller trial ([Nguyen 2017](#); [Savovic 2012](#)).

Despite all limitations, [Marra 2000](#) suggested that intravenous ceftriaxone could be an alternative to penicillin G for people with neurosyphilis; but it could be understood as a 'Texas sharpshooter fallacy', where the trial authors ignored differences but addressed similarities. Also, it is known that small trials could show larger benefits ([Zhang 2013](#)).

One limitation of the randomised clinical trial included in this systematic review was the lack of consistency in the measurement of the outcomes recorded as baseline characteristics, due to the fact that not all participants included in the trial received the same tests ([Marra 2000](#)). We noticed that the outcomes measured in [Marra 2000](#) could be affected by factors such as the methods used to measure the laboratory outcomes at the beginning of the treatment and during its follow-up, and the measurements of VDRL and RPR at baseline. We cannot know if the data reported here can be applied in other populations with other types of availability of resources to treat neurosyphilis, or even people without HIV. The lack of studies that address additional interventions limits our ability to make a clear statement related to treatment for neurosyphilis. At the same time, we cannot make any statement regarding the safety of the treatment for neurosyphilis due to the absence of adverse events in the report. In addition to the participants that did not finish the study, the trial authors were not able to measure CSF-VDRL and RPR titres in all participants who finished the trial, which is why we consider that those participants with unquantified CSF-VDRL and RPR should be considered as withdrawals from the trial.

Quality of the evidence

We used the GRADE approach in order to evaluate the quality of the evidence ([GRADEpro GDT 2015](#); [Schünemann 2017](#)). We downgraded the quality of the evidence by one level due to risk of bias. We downgraded by two levels due to imprecision because this study had a small sample size and very low number of events, which had an impact on the precision of the effect estimates, since not all the participants received the same test to establish serological cure and clinical cure, and adverse events were inappropriately reported. We did not downgrade for indirectness and publication bias.

See [Summary of findings for the main comparison](#) for details.

Potential biases in the review process

We performed an exhaustive search to identify and retrieve all published and unpublished clinical trials for the treatment of neurosyphilis in adults, unfortunately only one study met our inclusion criteria.

In all of the procedures in this review we followed the guidelines in the *Cochrane Handbook for Systematic Reviews of Interventions* ([Higgins 2011](#)), to prevent any bias throughout the review. We performed a wide search for trials, contacting trial authors, and locating all the full texts in order to develop a complete review

of trials. We did not limit the search by language or date. We considered the probability of missing trials as low despite only having identified one trial to be included in our review. In addition, we tried to contact the authors from the trial awaiting classification (Serragui 1999), however we could not obtain a response from them in order to determine the eligibility of this trial for inclusion.

Agreements and disagreements with other studies or reviews

The narrative review published by Clement 2014, based on observational and experimental studies, suggests that people with neurosyphilis should be managed with penicillin, and ceftriaxone should be used for people who are allergic to penicillin. However, the authors stated that the evidence of its efficacy is still limited (Clement 2014). Based on expert consensus, the CDC guidelines for Sexually Transmitted Diseases Treatment Guidelines recommend that the treatment for neurosyphilis should be aqueous crystalline penicillin G and, as an alternative treatment, procaine penicillin G or probenecid (CDC 2015). In our review we did not find evidence to support ceftriaxone use or other antibiotic interventions to treat neurosyphilis in adults.

AUTHORS' CONCLUSIONS

Implications for practice

Although the authors who published the only study included in this review state that ceftriaxone is an alternative to penicillin for the treatment of adults with neurosyphilis (Marra 2000), the

evidence we found is not clear and precise to support the use of ceftriaxone for neurosyphilis in adults. This conclusion is based on findings with a high risk of bias, imprecision of the outcomes evaluated, incomplete data reporting, and funding of the trial by the pharmaceutical industry. It is not possible to support or refute the ceftriaxone regime recommended to treat people with neurosyphilis. Also, the benefits to people without HIV and neurosyphilis are unknown, as is the ceftriaxone safety profile.

Implications for research

This Cochrane Review has identified a need for adequately powered, randomised clinical trials for assessing clinical effectiveness and harms of antibiotics for treating people with neurosyphilis. This would enable us to conduct a systematic review than would include more than one randomised clinical trial, which would allow us to present more conclusive results. Potential trials should be planned according to Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) recommendations and conducted and reported as recommended by the Consolidated Standards of Reporting Trials (CONSORT) statement. Furthermore, the outcomes should be based on patients' perspectives, taking into account Patient-Centered Outcomes Research Institute (PCORI) recommendations.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Marra 2000

Methods	Design: parallel (2 arms) Phase: NR Multicentre study: yes Country: USA International: no Follow-up period: 52 weeks Dates: October 1991-April 1994
Participants	Inclusion criteria

Marra 2000 (Continued)

- Patients infected with HIV-1 with syphilis
- Patients with serum RPR test titre $\geq 1:16$ confirmed with either MHA-TP test or a FTA-ABS test
- Patients with CSF abnormalities, including reactive CSF-VDRL test
- Patients with CSF WBC count $> 20/u/L$ or a CSF protein concentration $> 50 \text{ mg/dL}$

Exclusion criteria

- Patients treated for syphilis within 1 year before enrolment
- Patients that had received antibiotic therapy that would be active against *T Pallidum* within 45 days before enrolment
- Patients with other CNS documented infection (other than HIV-1) that could cause CSF abnormalities

Enrolled: 36

Randomised: 36 (ceftriaxone: 18; penicillin G: 18)

Age: 34 years (median) range (24-59)

Gender: overall male 87% (33/36)

- CSF WBC count $\geq 20/mL$ baseline: ceftriaxone: 5/14; penicillin G: 5/16
- CSF WBC count at baseline, cells/mL (median (range)): ceftriaxone: 8 (0-150); penicillin G: 14 (1-104)
- CSF protein level $\geq 50 \text{ mg/dL}$ at baseline: ceftriaxone: 12/14; penicillin G: 11/16
- CSF protein level at baseline, mg/dL (median (range)): ceftriaxone: 62 (40-202); penicillin G: 56 (25-323)
- Reactive CSF-VDRL at baseline: ceftriaxone: 7/10; penicillin G: 7/13
- Reciprocal CSF-VDRL titre at baseline (median (range)): ceftriaxone: 4 (1-64); penicillin G: 2 (1-8)
- Reciprocal serum RPR titre (median (range)): ceftriaxone: 192 (16-2048); penicillin G: 48 (16-512)

Withdrawals: ceftriaxone: 23% (4/18); penicillin: 12% (2/18)

Interventions	Ceftriaxone: 2 g IV once daily for 10 days Penicillin G: 4 MU IV every 4 h for 10 days
Outcomes	Primary <ul style="list-style-type: none"> • Improvement in CSF measures and in serum titres categorically as 1:4 fold decline in initially reactive CSF-VDRL or serum RPR titre or a reversion to non-reactivity • 10% decline from an initial CSF WBC count $> 20/u/L$ or in an initial CSF protein concentration $> 50 \text{ mg/dL}$
Notes	<ul style="list-style-type: none"> • Date trial conducted: October 1991-April 1994 • Trial ID number: NCT00000648 • Sample size estimation a priori: no • Sponsor: National Institutes of Health (NIH) Adult AIDS Clinical Trials Group; NIH (NS 34235 to C. M. M. and AI 27664 to P. B.); and Hoffmann-La Roche • Role of sponsors: not declared • Sponsored by drug company: yes. Hoffmann-La Roche • Conflicts of interest: not declared

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Participants were randomised to receive ceftriaxone or penicillin but the publication does not provide any details regarding the randomisation method.

Marra 2000 (Continued)

Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgment of 'low risk' or 'high risk'
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient information to permit judgment of 'low risk' or 'high risk'
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgment of 'low risk' or 'high risk'
Incomplete outcome data (attrition bias) All outcomes	High risk	Withdrawals: 17% (6/36) <ul style="list-style-type: none"> Ceftriaxone: (4/18) Penicillin: (2/18)
Selective reporting (reporting bias)	High risk	<ul style="list-style-type: none"> The trial authors did not describe the changes in all baseline characteristics described Also, they reported adverse events as symptoms and signs within clinical characteristics of participants Trial results published six years after the trial had finished, so long time interval between the conduct of the trial (1991-1994) and the time of publishing (2000)
Other bias	High risk	<ul style="list-style-type: none"> The trial authors did not calculate a sample size Industry bias

CSF: cerebrospinal fluid; **CNS:** central nervous system; **FTA-ABS:** fluorescent treponemal antibody absorbed; **IV:** intravenous; **NR:** not reported; **MHA-TP:** reactive microhemagglutination -*Treponema pallidum*; **RPR:** rapid plasma reagin; *T pallidum:* *Treponema pallidum*; **VDRL:** Venereal Disease Research Laboratory; **WBC:** white blood cell

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Chesney 1949	Literature review
Clement 2014	Review about syphilis treatment
Dunaway 2017	Not a randomised clinical trial
Goldman 1950	Review of a previous published report of 140 cases
Hahn 1952	Not a randomised clinical trial
Kopp 1949	Case series of 394 patients
Orban 1957	Case series of 254 patients
Philcox 1987	Not a randomised clinical trial
Potthoff 2009	This was a randomised, prospective, open-label trial. The trial authors reported that they had 2 cases of neurosyphilis but they did not describe their treatment and outcomes.

Study	Reason for exclusion
Rofls 1997	Included participants with primary and secondary syphilis
Short 1966	Literature review
Smith 2004	Did not include participants with neurosyphilis
Starzycki 1990	Not a randomised clinical trial
Tempski 1958	Review of a previous published report of 76 cases

Characteristics of studies awaiting assessment *[ordered by study ID]*

[Serragui 1999](#)

Methods	2 drug treatments were used, it is not clear if this study was a clinical trial
Participants	People with neurosyphilis
Interventions	Treatment A: penicillin G infusion for 4 h of 20 MU for 3 weeks Treatment B: penicillin G infusion for 6 h of 30 MU for 10 days
Outcomes	Not clear
Notes	We requested the full-text article from the authors but have not received it.

DATA AND ANALYSES

Comparison 1. Ceftriaxone versus penicillin G

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Serological cure	1	36	Risk Ratio (M-H, Random, 95% CI)	1.5 [0.28, 7.93]
2 Clinical cure	1	36	Risk Ratio (M-H, Random, 95% CI)	4.0 [0.98, 16.30]
3 All causes of withdrawals	1	36	Risk Ratio (M-H, Random, 95% CI)	2.0 [0.42, 9.58]

Analysis 1.1. Comparison 1 Ceftriaxone versus penicillin G, Outcome 1 Serological cure.

Study or subgroup	Ceftriaxone n/N	Penicillin G n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Marra 2000	3/18	2/18		100%	1.5[0.28,7.93]
			Favours ceftriaxone		Favours penicillin G

Analysis 1.2. Comparison 1 Ceftriaxone versus penicillin G, Outcome 2 Clinical cure.

Analysis 1.3. Comparison 1 Ceftriaxone versus penicillin G, Outcome 3 All causes of withdrawals.

APPENDICES

Appendix 1. Medical glossary

Term	Definition	Source
Aerobic	Using oxygen	Merriam webster dictionary (www.merriam-webster.com/dictionary/aerobic)
Anaerobic	Not using oxygen	Merriam webster dictionary (www.merriam-webster.com/dictionary/anaerobic)

(Continued)

Bacteriostasis	Inhibition of the growth of bacteria without destruction	Merriam webster dictionary (www.merriam-webster.com/dictionary/bacteriostasis)
Chancre	The primary sore of syphilis, a painless indurated, eroded papule, occurring at the site of entry of the infection	www.ncbi.nlm.nih.gov/mesh/?term=chancre
Fluorescent treponemal antibody (FTA)	Serological assay that detects antibodies to <i>Treponema pallidum</i> , the aetiologic agent of syphilis. After diluting the patient's serum to remove non-specific antibodies, the serum is mixed on a glass slide with Nichol's strain of <i>T pallidum</i> . An antigen-antibody reaction occurs if the test is positive and the bound antibodies are detected with fluorescent antihuman gamma-globulin antibody	www.ncbi.nlm.nih.gov/mesh/?term=FTA+(Fluorescent+Treponemal+Antibody)
Gummatous syphilis	Granulomatous, nodular lesions that can occur in a variety of organs, most commonly skin and bones	www.uptodate.com/contents/syphilis-epidemiology-pathophysiology-and-clinical-manifestations-in-hiv-uninfected-patients
Microhemagglutination assay (MHA-TP)	Hemagglutination tests are sensitive tests to measure certain antigens, antibodies, or viruses, using their ability to agglutinate certain erythrocytes	www.ncbi.nlm.nih.gov/mesh/?term=Hemagglutination+Tests
Primary syphilis	Following acquisition of <i>T pallidum</i> , the initial clinical manifestations are termed primary syphilis and usually consist of a chancre at the site of inoculation	/www.uptodate.com/contents/syphilis-epidemiology-pathophysiology-and-clinical-manifestations-in-hiv-uninfected-patients
Reagin	Antibodies, especially immunoglobulin E, that bind to tissue of the same species so that antigens induce release of histamine and other vasoactive agents. Hypersensitivity is the clinical manifestation	www.ncbi.nlm.nih.gov/mesh/?term=Reagin
Rapid plasma reagin (RPR)	The RPR test looks for antibodies that react to syphilis in the blood. This means the test doesn't detect <i>T pallidum</i> , the bacterium that causes syphilis. Instead, it looks for antibodies against substances released by cells harmed by <i>T pallidum</i>	www.urmc.rochester.edu/encyclopedia/content.aspx?contenttypeid=167&contentid=rapid_plasma_reagin_syphilis
Latent syphilis	Latent syphilis refers to the period during which people infected with <i>T pallidum</i> have no symptoms but have infection demonstrable by serological testing. Based upon the likelihood of spontaneous mucocutaneous relapses, this period has classically been separated into two categories: early latent and late latent syphilis. People in the early latent period are believed to be potentially infectious in contrast to late latency, when transmission is no longer likely	www.uptodate.com/contents/syphilis-epidemiology-pathophysiology-and-clinical-manifestations-in-hiv-uninfected-patients
Venereal Disease Research Laboratory test (VDRL)	The VDRL test is a screening test for syphilis. It measures antibodies that the body may produce if the person has come into contact with <i>T pallidum</i> bacteria	www.nlm.nih.gov/medlineplus/ency/article/003515.htm

Appendix 2. Operative characteristics of serological tests for *Treponema pallidum*

Test	Performance	Source
Fluorescent treponemal antibody absorption test (FTA ABS)	Sensitivity of 84% in primary stage, secondary stage 100%, latent 100% and late syphilis 96%	CDC 2015
Serum microhemagglutination– <i>Treponema pallidum</i> (MHA-TP)	Sensitivity of 88% in primary stage, secondary stage 100%, latent 100%	CDC 2015
Non-treponemal test like rapid plasma reagin (RPR)	Sensitivity of 86% in primary stage, secondary stage 100%, latent 98% and late syphilis 73%	CDC 2015
Venereal Disease Research Laboratory (VDRL)	Sensitivity of 78% in primary stage, secondary stage 100%, latent 95% and late syphilis 71%	CDC 2015

Appendix 3. Diagnostic criteria for neurosyphilis in the phase of HIV infection

Source: [Berger 2014](#)

Definite neurosyphilis defined as:

- positive blood treponemal serology, for example, fluorescent treponemal antibody absorption test (FTA-ABS), microhemagglutination–*Treponema pallidum* (MHA-TP);
- positive cerebrospinal fluid Venereal Disease Research Laboratory test (CSF-VDRL).

Probable neurosyphilis defined as:

- positive blood treponemal serology;
- negative CSF VDRL;
- CSF mononuclear pleocytosis (> 20 cells/mm³) or positive CSF protein (> 60 mg/dL);
- neurological complications compatible with neurosyphilis, such as cranial nerve palsies, stroke, or evidence of ophthalmological syphilis.

Possible neurosyphilis defined as:

- positive blood treponemal serology;
- negative CSF VDRL;
- CSF mononuclear pleocytosis (> 20 cells/mm³) or positive CSF protein (> 60 mg/dL);
- no neurological or ophthalmological complications compatible with syphilis.

Appendix 4. Electronic search strategies

CENTRAL and MEDLINE (Ovid platform)

1. exp Neurosyphilis/
2. neurosyphilis.tw.
3. (lues adj5 cerebrospinal).tw.
4. (nervous adj5 syphilis).tw.
5. neurolues.tw.
6. (syphilis adj5 nervous adj5 system).tw.
7. (syphilis adj5 cns).tw.
8. exp Tabes Dorsalis/
9. (tabes adj5 dorsalis).tw.
10. (tabes adj5 spinalis).tw.
11. myelosyphilis.tw.
12. (spinal adj5 syphilis).tw.
13. or/1-12

- 14.exp Anti-Bacterial Agents/
- 15.anti bacterial\$.tw.
- 16.antibacterial\$.tw.
- 17.antibiotic\$.tw.
- 18.bacteriocid\$.tw.
- 19.bactericid\$.tw.
- 20.exp Anti-Infective Agents/
- 21.anti infective\$.tw.
- 22.antiinfective\$.tw.
- 23.microbicid\$.tw.
- 24.antimicrobial\$.tw.
- 25.anti microbial\$.tw.
- 26.exp beta-Lactams/
- 27.exp Penicillins/
- 28.exp Penicillin G/
- 29.exp Penicillin G Procaine/
- 30.exp Penicillin G Benzathine/
- 31.exp Amoxicillin/
- 32.(beta adj1 lactam\$).tw.
- 33.penicilli\$.tw.
- 34.amoxicillin.tw.
- 35.exp Cephalosporins/
- 36.cephalosporin\$.tw.
- 37.exp Ceftriaxone/
- 38.ceftriaxon\$.tw.
- 39.exp Tetracyclines/
- 40.exp Tetracycline/
- 41.tetracyclin\$.tw.
- 42.exp Doxycycline/
- 43.doxycycline.tw.
- 44.exp Minocycline/
- 45.minocycline.tw.
- 46.glycylcycline.tw.
- 47.tigecycline.tw.
- 48.exp Macrolides/
- 49.macrolide\$.tw.
- 50.exp Erythromycin/
- 51.erythromycin.tw.
- 52.exp Azithromycin/
- 53.azithromycin.tw.
- 54.exp Clarithromycin/
- 55.clarithromycin.tw.
- 56.exp Ketolides/
- 57.ketolides.tw.
- 58.telithromycin.tw.
- 59.or/14-58
- 60.randomised controlled trial.pt.
- 61.controlled clinical trial.pt.
- 62.randomized.ab.
- 63.placebo.ab.
- 64.clinical trials as topic.sh.
- 65.randomly.ab.

- 66.trial.ti.
- 67.or/60-66
- 68.exp animals/ not humans.sh.
- 69.67 not 68
- 70.13 and 59 and 69

Note: the CENTRAL search strategy does not include terms #60 to #69.

Embase.com (Elsevier)

1. 'neurosyphilis'/exp
2. neurosyphilis:ab,ti
3. (lues NEAR/5 cerebrospinalis):ab,ti
4. (nervous NEAR/5 syphilis):ab,ti
5. neurolues:ab,ti
6. (syphilis):ab,ti AND (nervous NEAR/5 system):ab,ti
7. (syphilis NEAR/5 cns):ab,ti
8. 'tabes dorsalis'/exp
9. (tabes NEAR/5 dorsalis):ab,ti
10. (tabes NEAR/5 spinalis):ab,ti
11. myelosyphilis:ab,ti
12. (spinal NEAR/5 syphilis):ab,ti
13. or/1-12
14. 'antiinfective agent'/exp
15. antiinfective*:ab,ti
16. (anti NEAR/5 infective*):ab,ti
17. antibacterial*:ab,ti
18. (anti NEAR/5 bacterial*):ab,ti
19. antimicrobial*:ab,ti
20. (anti NEAR/5 microbial*):ab,ti
21. 'antimicrobial therapy'/exp
22. 'antibiotic agent'/exp
23. antibiotic*:ab,ti
24. 'bactericide'/exp
25. bactericid*:ab,ti
26. bacteriocid*:ab,ti
27. 'microbicide'/exp
28. microbicid*:ab,ti
29. 'beta lactam'/exp
30. 'penicillin derivative'/exp
31. 'penicillin G'/exp
32. 'procaine penicillin'/exp
33. 'benzathine penicillin'/exp
34. 'penicillin G potassium plus probenecid'/exp
35. 'amoxicillin'/exp
36. 'beta lactam':ab,ti
37. penicilli*:ab,ti
38. amoxicillin:ab,ti
39. 'cephalosporin derivative'/exp
40. cephalosporin*:ab,ti
41. 'ceftriaxone'/exp
42. ceftriaxon*:ab,ti
43. 'tetracycline derivative'/exp
44. 'tetracycline'/exp
45. tetracyclin*:ab,ti
46. 'doxycycline'/exp
47. doxycycline:ab,ti
48. 'minocycline'/exp
49. minocycline:ab,ti
50. 'glycylcycline derivative'/exp
51. glycylcycline:ab,ti
52. 'tigecycline'/exp

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53. tigecycline:ab,ti
 54. 'macrolide'/exp
 55. macrolide*:ab,ti
 56. 'erythromycin'/exp
 57. erythromycin:ab,ti
 58. 'azithromycin'/exp
 59. azithromycin:ab,ti
 60. 'clarithromycin'/exp
 61. clarithromycin:ab,ti
 62. 'ketolide'/exp
 63. ketolide*:ab,ti
 64. 'telithromycin'/exp
 65. telithromycin:ab,ti
 66. or/14-66
 67.1 'randomised controlled trial'/exp
 67.2 'single blind procedure'/exp
 67.3 'double blind procedure'/exp
 67.4 'crossover procedure'/exp
 67.5 #36.1 OR #36.2 OR #36.3 OR #36.4
 67.6 random*:ab,ti
 67.7 placebo*:ab,ti
 67.8 allocat*:ab,ti
 67.9 crossover*:ab,ti
 67.10 'cross over':ab,ti
 67.11 trial:ti
 67.12 (doubl* NEXT/1 blind*):ab,ti
 67.13 #67.6 OR #67.7 OR #67.8 OR #67.9 OR #67.10 OR #67.11 OR #67.12
 67.14 #67.5 OR #67.13
 67.15 'animal'/de
 67.16 'animal experiment'/de
 67.17 'nonhuman'/de
 67.18 #67.15 OR #67.16 OR #67.17
 67.19 'human'/de
 67.20 #67.18 AND #67.19
 67.21 #67.18 NOT #67.20
 67.22 #67.14 NOT #67.21
 68. #13 AND #66 AND #67 AND [embase]/lim

LILACS (iAHx interface)

(mh:("Neurosyphilis")) OR (ti:("neurosyphilis")) OR (ab:("neurosyphilis")) AND db:("LILACS") AND type_of_study:("clinical_trials")

WHO International Clinical Trials Registry Platform ICTRP portal

neurosyphilis OR tabes dorsal

ClinicalTrials.gov

neurosyphilis OR tabes dorsal

Appendix 5. Electronic search strategies update

Electronic search Report No. 1	
Type of search	Update
Database	§ MEDLINE
	§ MEDLINE In-Process & Other Non-Indexed Citations
	§ MEDLINE Daily Update

(Continued)

Platform	Ovid
Search date	25 May 2018
Range of search date	2014-current
Language Restrictions	None
Other Limits	None
Search strategy (results)	1 exp Neurosyphilis/ (3708) 2 neurosyphilis.tw. (1878) 3 (lues adj5 cerebrospinal).tw. (5) 4 (nervous adj5 syphilis).tw. (105) 5 neurolues.tw. (31) 6 (syphilis adj5 nervous adj5 system).tw. (93) 7 (syphilis adj5 cns).tw. (21) 8 exp Tabes Dorsalis/ (698) 9 (tabes adj5 dorsalis).tw. (271) 10 (tabes adj5 spinalis).tw. (0) 11 myelosyphilis.tw. (0) 12 (spinal adj5 syphilis).tw. (25) 13 or/1-12 (4155) 14 exp Anti-Bacterial Agents/ (695595) 15 anti bacterial\$.tw. (2405) 16 antibacterial\$.tw. (57619) 17 antibiotic\$.tw. (272269) 18 bacteriocid\$.tw. (533) 19 bactericid\$.tw. (26584) 20 exp Anti-Infective Agents/ (1556656) 21 anti infective\$.tw. (3308) 22 antiinfective\$.tw. (426) 23 microbicid\$.tw. (5471) 24 antimicrobial\$.tw. (122743) 25 anti microbial\$.tw. (2972) 26 exp beta-Lactams/ (124482) 27 exp Penicillins/ (78933) 28 exp Penicillin G/ (37936)

(Continued)

- 29 exp Penicillin G Procaine/ (1774)
- 30 exp Penicillin G Benzathine/ (1835)
- 31 exp Amoxicillin/ (10798)
- 32 (beta adj1 lactam\$.tw. (36016)
- 33 penicilli\$.tw. (59832)
- 34 amoxicillin.tw. (12307)
- 35 exp Cephalosporins/ (41099)
- 36 cephalosporin\$.tw. (19361)
- 37 exp Ceftriaxone/ (5679)
- 38 ceftriaxon\$.tw. (8794)
- 39 exp Tetracyclines/ (46666)
- 40 exp Tetracycline/ (19570)
- 41 tetracyclin\$.tw. (32075)
- 42 exp Doxycycline/ (9210)
- 43 doxycycline.tw. (11150)
- 44 exp Minocycline/ (5697)
- 45 minocycline.tw. (5653)
- 46 glycylicycline.tw. (192)
- 47 tigecycline.tw. (2395)
- 48 exp Macrolides/ (104975)
- 49 macrolide\$.tw. (13649)
- 50 exp Erythromycin/ (24271)
- 51 erythromycin.tw. (18866)
- 52 exp Azithromycin/ (4763)
- 53 azithromycin.tw. (6541)
- 54 exp Clarithromycin/ (6017)
- 55 clarithromycin.tw. (7827)
- 56 exp Ketolides/ (791)
- 57 ketolides.tw. (339)
- 58 telithromycin.tw. (807)
- 59 or/14-58 (1741849)
- 60 randomised controlled trial.pt. (0)
- 61 controlled clinical trial.pt. (93018)
- 62 randomized.ab. (382168)

(Continued)

63 placebo.ab. (179115)
64 clinical trials as topic.sh. (186743)
65 randomly.ab. (264939)
66 trial.ti. (169927)
67 or/60-66 (980220)
68 exp animals/ not humans.sh. (4571896)
69 67 not 68 (888109)
70 13 and 59 and 69 (18)
71 limit 70 to yr="2014 -Current" (4)

Number of references identified

4

Electronic search Report No. 2

Type of search Update

Database EMBASE

Platform EMBASE.com

Search date 25 May 2018

Range of search date 2014-current

Language Restrictions None

Other Limits None

Search strategy (results)

#1 'neurosyphilis'/exp 4221
#2 neurosyphilis:ab,ti 2595
#3 (lues NEAR/5 cerebrospinalis):ab,ti 2
#4 (nervous NEAR/5 syphilis):ab,ti 141
#5 neurolues:ab,ti 57
#6 syphilis:ab,ti AND ((nervous NEAR/5 system):ab,ti) 445
#7 (syphilis NEAR/5 cns):ab,ti 36
#8 'tabes dorsalis'/exp 827
#9 (tabes NEAR/5 dorsalis):ab,ti 361
#10 (tabes NEAR/5 spinalis):ab,ti 0
#11 myelosyphilis:ab,ti 0

(Continued)

- #12 (spinal NEAR/5 syphilis):ab,ti 37
- #13 OR/1-12 5498
- #14 'antiinfective agent'/exp 3408288
- #15 antiinfective*:ab,ti 972
- #16 (anti NEAR/5 infective*):ab,ti 5483
- #17 antibacterial*:ab,ti 90090
- #18 (anti NEAR/5 bacterial*):ab,ti 6112
- #19 antimicrobial*:ab,ti 190285
- #20 (anti NEAR/5 microbial*):ab,ti 6386
- #21 'antimicrobial therapy'/exp 198173
- #22 'antibiotic agent'/exp 1431811
- #23 antibiotic*:ab,ti 411262
- #24 'bactericide'/exp 2501
- #25 bactericid*:ab,ti 34155
- #26 bacteriocid*:ab,ti 694
- #27 'microbicide'/exp 1949
- #28 microbicid*:ab,ti 7009
- #29 'beta lactam'/exp 6130
- #30 'penicillin derivative'/exp 301688
- #31 'penicillin g'/exp 81082
- #32 'procaine penicillin'/exp 4574
- #33 'benzathine penicillin'/exp 5862
- #34 'penicillin g potassium plus probenecid'/exp 0
- #35 'amoxicillin'/exp 59081
- #36 'beta lactam':ab,ti 5639
- #37 penicilli*:ab,ti 78187
- #38 amoxicillin:ab,ti 20695
- #39 'cephalosporin derivative'/exp 215707
- #40 cephalosporin*:ab,ti 28410
- #41 'ceftriaxone'/exp 55019
- #42 ceftriaxon*:ab,ti 15362
- #43 'tetracycline derivative'/exp 165771
- #44 'tetracycline'/exp 81551
- #45 tetracyclin*:ab,ti 40642

(Continued)

- #46 'doxycycline'/exp 49124
- #47 doxycycline:ab,ti 17868
- #48 'minocycline'/exp 22732
- #49 minocycline:ab,ti 8500
- #50 'glycylcycline derivative'/exp 342
- #51 glycylcycline:ab,ti 293
- #52 'tigecycline'/exp 9222
- #53 tigecycline:ab,ti 4185
- #54 'macrolide'/exp 287268
- #55 macrolide*:ab,ti 19796
- #56 'erythromycin'/exp 72658
- #57 erythromycin:ab,ti 24226
- #58 'azithromycin'/exp 32205
- #59 azithromycin:ab,ti 11436
- #60 'clarithromycin'/exp 34957
- #61 clarithromycin:ab,ti 12825
- #62 'ketolide'/exp 3606
- #63 ketolide*:ab,ti 856
- #64 'telithromycin'/exp 2813
- #65 telithromycin:ab,ti 1048
- #66 OR/14-65 3606218
- #67 'randomized controlled trial'/exp 545127
- #68 'single blind procedure'/exp 34641
- #69 'double blind procedure'/exp 159671
- #70 'crossover procedure'/exp 58691
- #71 OR/67-70 611329
- #72 random*:ab,ti 1394760
- #73 placebo*:ab,ti 287738
- #74 allocat*:ab,ti 137736
- #75 crossover*:ab,ti 70044
- #76 'cross over':ab,ti 30400
- #77 trial:ti 273064
- #78 (doubl* NEXT/1 blind*):ab,ti 198338
- #79 OR/72-78 1704898

(Continued)

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#80 #71 OR #79 1804666
#81 'animal'/de 1890747
#82 'animal experiment'/de 2353546
#83 'nonhuman'/de 5770845
#84 #81 OR #82 OR #83 7984696
#85 'human'/de 20440775
#86 #84 AND #85 1872104
#87 84 NOT 86 1357450
#88 #80 NOT #87 1696193
#89 #13 AND #66 AND #88 25
#90 #89 AND [embase]/lim NOT ([embase]/lim AND [medline]/lim) 9
#91 #89 AND [embase]/lim NOT ([embase]/lim AND [medline]/lim) AND (2017:py OR 2018:py) 2
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Number of references identified	16
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Electronic search Report No. 3

Type of search	Update
Database	Cochrane Central Register of Controlled Trials
Platform	Ovid
Search date	07/12/2014
Range of search date	From inception
Language Restrictions	None
Other Limits	None

Search strategy (results)	1 exp Neurosyphilis/ (8) 2 neurosyphilis.tw. (35) 3 (lues adj5 cerebrospinalis).tw. (0) 4 (nervous adj5 syphilis).tw. (6) 5 neurolues.tw. (0) 6 (syphilis adj5 nervous adj5 system).tw. (6) 7 (syphilis adj5 cns).tw. (0) 8 exp Tabes Dorsalis/ (0)
----------------------------------	--

(Continued)

- 9 (tabes adj5 dorsalis).tw. (3)
- 10 (tabes adj5 spinalis).tw. (0)
- 11 myelosyphilis.tw. (0)
- 12 (spinal adj5 syphilis).tw. (1)
- 13 or/1-12 (47)
- 14 exp Anti-Bacterial Agents/ (26382)
- 15 (anti adj5 bacterial\$).tw. (187)
- 16 antibacterial\$.tw. (2441)
- 17 antibiotic\$.tw. (24056)
- 18 bacteriocid\$.tw. (25)
- 19 bactericid\$.tw. (1337)
- 20 exp Anti-Infective Agents/ (62043)
- 21 (anti adj5 infective\$).tw. (260)
- 22 antiinfective\$.tw. (36)
- 23 microbicid\$.tw. (400)
- 24 antimicrobial\$.tw. (6131)
- 25 (anti adj5 microbial\$).tw. (179)
- 26 exp beta-Lactams/ (8880)
- 27 exp Penicillins/ (5283)
- 28 exp Penicillin G/ (4339)
- 29 exp Penicillin G Procaine/ (112)
- 30 exp Penicillin G Benzathine/ (101)
- 31 exp Amoxicillin/ (2594)
- 32 (beta adj5 lactam\$).tw. (1206)
- 33 penicilli\$.tw. (2323)
- 34 amoxicillin.tw. (3971)
- 35 exp Cephalosporins/ (4152)
- 36 cephalosporin\$.tw. (1324)
- 37 exp Ceftriaxone/ (673)
- 38 ceftriaxon\$.tw. (1330)
- 39 exp Tetracyclines/ (2304)
- 40 exp Tetracycline/ (772)
- 41 tetracyclin\$.tw. (1751)
- 42 exp Doxycycline/ (967)

(Continued)

- 43 doxycycline.tw. (1711)
- 44 exp Minocycline/ (454)
- 45 minocycline.tw. (861)
- 46 glycylicycline.tw. (16)
- 47 tigecycline.tw. (132)
- 48 exp Macrolides/ (7751)
- 49 macrolide\$.tw. (919)
- 50 exp Erythromycin/ (3080)
- 51 erythromycin.tw. (1717)
- 52 exp Azithromycin/ (834)
- 53 azithromycin.tw. (2121)
- 54 exp Clarithromycin/ (1353)
- 55 clarithromycin.tw. (2754)
- 56 exp Ketolides/ (46)
- 57 ketolides.tw. (11)
- 58 telithromycin.tw. (119)
- 59 or/14-58 (88155)
- 60 13 and 59 (28)
- 61 limit 60 to yr="2014 -Current" (6)

Number of references identified 6

CONTRIBUTIONS OF AUTHORS

Diana Buitrago (DB) is the contact person of this review. DB co-ordinated the contributions from the co-authors and wrote the final draft of the review.

DB, Arturo J Martí-Carvajal (AMC), and Lucien O Conterno (LOC) worked on the methods sections. DB, LOC, Adriana Jimenez (AJ) and Rodrigo Pardo (RP) drafted the clinical sections of the background section.

All the review authors contributed to writing the review.

DECLARATIONS OF INTEREST

DB has no known conflicts of interest.

AMC has no known conflicts of interest.

AJ In 2016 and 2017 received payment for lectures from Procaps and Abbott laboratories. This activity was not related to her work with The Cochrane Collaboration or any Cochrane Review.

LOC has no known conflicts of interest.

RP has no known conflicts of interest.

SOURCES OF SUPPORT

Internal sources

- Fundación Universitaria de Ciencias de la Salud, Hospital San José/Hospital Infantil de San José, Colombia.

Academic and financial

External sources

- Iberoamerican Cochrane Center, Spain.

Academic

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We changed the type of interventions. Instead of considering the β -lactam group as the control group, we considered any antibiotic regime compared to any other antibiotic regime. The search strategy was performed in Medline Ovid 1946 to present which has a full coverage that includes all data bases mentioned in the protocol (MEDLINE, Ovid platform: inception to present, MEDLINE In-Process & Other Non-Indexed Citations and, MEDLINE Daily Update, Ovid platform: inception to present)

Because we only identified one study in this systematic review with limited information, we could not apply the following methods.

- Analysis of other antibiotic regimes apart from ceftriaxone or Penicillin G
- Assessment of adverse events (primary outcome), recurrence of neurosyphilis, time to recovery and quality of life (secondary outcomes)
- Analysis of continuous data
- Unit of analysis issues
- Methods to assess heterogeneity
- Methods to assess reporting bias
- Methods to synthesise data
- Subgroup analysis
- TSA analysis: We were unable to perform TSA due to very small sample size and very low number of serological cure, clinical cure and adverse events. We had projected to conduct a TSA using the following boundaries: 20% of relative risk reduction of proportion of experimental group, 5% for Alpha and 20 for Beta. For future updates we will try to conduct TSA, if new trials are available (CTU 2011).

INDEX TERMS

Medical Subject Headings (MeSH)

Anti-Bacterial Agents [*therapeutic use]; Ceftriaxone [therapeutic use]; Neurosyphilis [*drug therapy]; Randomized Controlled Trials as Topic

MeSH check words

Adult; Female; Humans; Male