

Antibiotikabehandling ved nevroborreliose

Notat fra Kunnskapsenteret
Litteratursøk med sortering
Mars 2011

 kunnskapsenteret

Bakgrunn: Nasjonalt kunnskapsenter for helsetjenesten fikk i oppdrag fra Helsedirektoratet å utføre et systematisk litteratursøk med påfølgende sortering av mulig relevante publikasjoner. Oppdraget var å finne litteratur/forskning om antibiotikabehandling ved nevroborreliose. **Metode:** Vi utarbeidet et systematisk litteratursøk. Det ble søkt i medisinske databaser etter litteratur, retningslinjer og behandlingsanbefalinger. Søket ble utført i februar 2011. Minst to forskere gikk uavhengig av hverandere gjennom identifiserte publikasjoner/referanser og vurderte relevans i forhold til inklusjonskriteriene. **Resultater:** • Vi identifiserte totalt 767 referanser. Av disse var 20 mulig relevante. • Referansene ble sortert i kategoriene: evidensbaserte retningslinjer, systematiske oversikter, randomiserte kontrollerte studier og studier med ukjent design. • Tre treff i elektroniske kliniske oppslagsverk er sortert separat.

Nasjonalt kunnskapssenter for helsetjenesten
Postboks 7004, St. Olavs plass
N-0130 Oslo
(+47) 23 25 50 00
www.kunnskapssenteret.no
Notat: ISBN 978-82-8121-398-2

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 kunnskapssenteret

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Institusjon Nasjonalt kunnskapssenter for helsetjenesten

Ansvarlig John-Arne Røttingen, direktør

Forfattere Ringerike, Tove, *seniorforsker, Nasjonalt kunnskapssenter for helsetjenesten*

Sæterdal, Ingvil, *seniorforsker, Nasjonalt kunnskapssenter for helsetjenesten*

Gundersen, Malene W., *bibliotekar, Helsedirektoratet*

Sundal, Jon, *overlege, Stavanger universitetssykehus*

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Nøkkelord Antibiotika, nevroborreliose, borrelia

Sitering Ringerike, T., Sæterdal, I., Gundersen, M.W., Sundal, J. Antibiotika ved nevroborreliose – systematisk litteratursøk med sortert referanseliste. Notat–2011. Oslo: Nasjonalt kunnskapssenter for helsetjenesten, 2011.

Nasjonalt kunnskapssenter for helsetjenesten fremskaffer og formidler kunnskap om effekt av metoder, virkemidler og tiltak og om kvalitet innen alle deler av helsetjenesten. Målet er å bidra til gode beslutninger slik at brukerne får best mulig helsetjenester.

Kunnskapssenteret er formelt et forvaltningsorgan under Helsedirektoratet, men har ingen myndighetsfunksjoner og kan ikke instrueres i faglige spørsmål.

Nasjonalt kunnskapssenter for helsetjenesten

Oslo, Mars 2011

Hovedfunn

Nasjonalt kunnskapssenter for helsetjenesten fikk i oppdrag fra Helsedirektoratet å utføre et systematisk litteratursøk med påfølgende sortering av mulig relevante publikasjoner. Oppdraget var å finne litteratur/forskning om antibiotikabehandling ved nevroborreliose.

Metode

Vi utarbeidet et systematisk litteratursøk. Det ble søkt i medisinske databaser etter litteratur, retningslinjer og behandlingsanbefalinger. Søket ble utført i februar 2011. Minst to forskere gikk uavhengig av hverandere gjennom identifiserte publikasjoner/referanser og vurderte relevans i forhold til inklusjonskriteriene.

Resultater

- Vi identifiserte totalt 767 referanser. Av disse var 20 mulig relevante.
- Referansene ble sortert i kategoriene: evidensbaserte retninglinjer, systematiske oversikter, randomiserte kontrollerte studier og studier med ukjent design.
- Tre treff i elektroniske kliniske oppslagsverk er sortert separat.

Tittel:

Antibiotikabehandling ved nevroborreliose – systematisk litteratursøk med sortert referanseliste

Publikasjonstype:

Litteratursøk med sortering

Litteratursøk med sortering er resultatet av å

- søke etter relevant litteratur ifølge en søkestrategi og
- eventuelt sortere denne litteraturen i grupper presentert med referanser og vanligvis sammendrag

Svarer ikke på alt:

- Ingen kritisk vurdering av studienes kvalitet
- Ingen analyse eller sammenfatning av studiene
- Ingen anbefalinger

Hvem står bak denne publikasjonen?

Kunnskapssenteret har gjennomført oppdraget etter forespørsel fra Helsedirektoratet

Når ble litteratursøket utført?

Søk etter studier ble avsluttet Februar 2011.

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Forord

Nasjonalt kunnskapssenter for helsetjenesten og Helsedirektoratet fikk i oppdrag fra Unn Ljøstad ved Sørlandet sykehus HF å finne litteratur om antibiotikabehandling av nevroborreliose (akutt, kronisk, tidlig, sen, Perifere nervesystem (PNS) og sentralnervesystemet (CNS)). Oppdragsgiver er deltaker i arbeidet med nasjonale antibiotikaretningslinjer for sykehus som lages i regi av Helsedirektoratet. Denne oversikten er tenkt som en liste over litteratur som kan være relevant dokumentasjonsgrunnlag for de nye nasjonale retningslinjene.

Prosjektgruppen har bestått av:

- Tove Ringerike, seniorforsker, Kunnskapssenteret
- Ingvil Sæterdal, seniorforsker, Kunnskapssenteret
- Malene W. Gundersen, bibliotekar, Helsedirektoratet
- Jon Sundal, overlege, Stavanger universitetssykehus

Gro Jamtvedt
Avdelingsdirektør

Marianne Klemp
Seksjonsleder

Ingvil Sæterdal
Prosjektleder

Innledning

Styrker og svakheter ved litteratursøk med sortering

Ved litteratursøk gjennomfører vi systematiske litteratursøk for en gitt problemstilling. Resultatene fra søket blir i sin helhet overlevert oppdragsgiver, eller vi kan videre også gjennomgå søkeresultatet og sortere ut ikke-relevante artikler. Dette gjøres basert på tittel og eventuelt sammendrag. Artiklene innhentes ikke i fulltekst. Manglende innhenting av artikler i fulltekst gjør at vi kan ha inkludert titler som vil vise seg ikke å være relevante ved gjennomlesning av fulltekst. Vi benytter kun databaser for identifisering av litteratur og kan derfor ha gått glipp av potensielt relevante studier. Andre måter å identifisere studier på som søk i referanselister, kontakt med eksperter på fagfeltet og upublisert litteratur blir ikke utført i dette oppdraget. Vi gjennomfører ingen kvalitetsvurdering av artiklene.

I enn systematisk oversikt eller HTA rapport ville vi videre innhentet artiklene i fulltekst for endelig vurdering opp mot inklusjonskriteriene. Inkluderte studier ville blitt kvalitetsvurdert i henhold til våre sjekklister. Resultater ville blitt sammenstilt og diskutert.

Begrunnelse for valg av søkestrategi

Vi har søkt i elektroniske kilder, men ikke etter grå litteratur eller liknende. Søket er gjort for hele tidsperioden databasen dekker bakover i tid, da antibiotikabehandling ikke er et nytt fagfelt. I søkene er det ikke lagt på filter for å begrense til spesielle studiedesign.

Problemstilling

I prosjektet har vi søkt etter litteratur som skal belyse problemstillinger knyttet til antibiotikabehandling av nevroborreliose i akutt, kronisk, tidlig og sen fase med tilhørende innvirkning på det perifere nervesystem (PNS) og sentralnervesystemet (CNS).

Det betyr at vi ikke søker etter litteratur knyttet til borreliaindusert artritt eller problemstillinger knyttet til tidligere manifestasjoner som erythema migrans eller kronisk lyme disease.

Metode

Litteratursøking

Vi søkte systematisk etter litteratur i følgende bibliografiske databaser:

- Embase
- Medline
- Cochrane Library
- CRD

Forskningsbibliotekar Malene W. Gundersen planla og utførte samtlige søk. Den fullstendige søkestrategien er vist i vedlegg. Søk etter studier ble avsluttet februar 2011.

Vi la bestillingen til grunn ved utarbeiding av litteratursøket og søkte etter artikler som oppfylte våre inklusjonskriterier for populasjon og intervensjon. Det ble ikke brukt filter for ulike studiedesign i søkene.

Vi utførte i tillegg søk i utvalgte elektroniske kliniske oppslagsverk som skal være evidensbaserte (Best Practice, Clinical Evidence, UpToDate) og databaser over retningslinjer (National Guidelines Clearinghouse, G-I-N). Fullstendig liste er gjengitt i vedlegg.

Inklusjonskriterier

Populasjon:	Voksne pasienter med nevroborreliose
Tiltak:	Behandling med antibiotika, ulike doser og varighet
Sammenlikning:	Behandling med antibiotika, ulike doser og varighet
Utfall:	Ikke presisert
Studiedesign	Systematiske oversikter, retningslinjer som baserer seg på systematiske søk/oversikter, randomiserte kontrollerte studier
Språk:	Ikke presisert

Artikkelutvelging

To forskere gikk gjennom alle titler og sammendrag for å vurdere relevans i henhold til inklusjonskriteriene. Vurderingene ble gjort uavhengig av hverandre og sammenlignet i etterkant. Der det var uenighet om vurderingene, ble inklusjon eller eksklusjon avgjort ved konsensus.

Utvelgelse av litteratur ble kun gjort basert på tittel og sammendrag. Vi bestilte ikke fulltekst av artiklene.

Resultat

Resultat av søk

Søket resulterte i 767 referanser fra bibliografiske databaser. Vi vurderte 20 av de identifiserte referansene til å være mulig relevante i henhold til inklusjonskriteriene.

Hovedårsaken til eksklusjon var at publikasjonene ikke oppfylte inklusjonskriteriene for studiedesign (randomisert kontrollert studie eller systematiske oversikter?) eller at oversiktsartiklene ikke redegjorde for en systematisk metode for identifisering av litteratur.

Resultat av sorteringen

Vi sorterte referansene i fire kategorier ut fra hvilket studiedesign de så ut til å ha (se tab 1). Vi presenterer referansene sortert i de ulike kategoriene og listet alfabetisk etter førsteforfatter innen hver kategori. Vi oppgir forfattere, tittel på publikasjonen, publikasjonssted og sammendrag av artikkelen slik de fremkom i de bibliografiske databasene.

Til slutt oppgir vi treffene vi fant i de elektroniske kliniske oppslagsverkene.

Tabell 1: Antall artikler sortert etter artikkeltype

Artikkeltype	Antall referanser:
Evidensbasert retningslinje	3
Systematisk oversikt	5
Randomisert kontrollert studie	7
Ukjent artikkeltype	5

Evidensbaserte retningslinjer

Halperin JJ, Shapiro ED, Logigian E, Belman AL, Dotevall L, Wormser GP, et al. Practice parameter: Treatment of nervous system Lyme disease (an evidence-based review): Report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology* 2007;69(1):91-102.

Ref ID: 157

Abstract: OBJECTIVE: To provide evidence-based recommendations on the treatment of nervous system Lyme disease and post-Lyme syndrome. Three questions were addressed: 1) Which antimicrobial agents are effective? 2) Are different regimens preferred for different manifestations of nervous system Lyme disease? 3) What duration of therapy is needed? METHODS: The authors analyzed published studies (1983-2003) using a structured review process to classify the evidence related to the questions posed. RESULTS: The panel reviewed 353 abstracts which yielded 112 potentially relevant articles that were reviewed, from which 37 articles were identified that were included in the analysis. CONCLUSIONS: There are sufficient data to conclude that, in both adults and children, this nervous system infection responds well to penicillin, ceftriaxone, cefotaxime, and doxycycline (Level B recommendation). Although most studies have used parenteral regimens for neuroborreliosis, several European studies support use of oral doxycycline in adults with meningitis, cranial neuritis, and radiculitis (Level B), reserving parenteral regimens for patients with parenchymal CNS involvement, other severe neurologic symptomatology, or failure to respond to oral regimens. The number of children (≥ 8 years of age) enrolled in rigorous studies of oral vs parenteral regimens has been smaller, making conclusions less statistically compelling. However, all available data indicate results are comparable to those observed in adults. In contrast, there is no compelling evidence that prolonged treatment with antibiotics has any beneficial effect in post-Lyme syndrome (Level A). 2007AAN Enterprises, Inc

Mygland A, Ljostad U, Fingerle V, Rupprecht T, Schmutzhard E, Steiner I. EFNS guidelines on the diagnosis and management of European Lyme neuroborreliosis. *Eur J Neurol* 2010;17(1):8-16.

Ref ID: 13

Abstract: Background: Lyme neuroborreliosis (LNB) is a nervous system infection caused by *Borrelia burgdorferi sensu lato* (Bb). Objectives: To present evidence-based recommendations for diagnosis and treatment. Methods: Data were analysed according to levels of evidence as suggested by EFNS. Recommendations: The following three criteria should be fulfilled for definite LNB, and two of them for possible LNB: (i) neurological symptoms; (ii) cerebrospinal fluid (CSF) pleocytosis; (iii) Bb-specific antibodies produced intrathecally. PCR and CSF culture may be corroborative if symptom duration is < 6 weeks, when Bb antibodies may be absent. PCR is otherwise not recommended. There is also not enough evidence to recommend the following tests for diagnostic purposes: microscope-based assays, chemokine CXCL13, antigen detection, immune complexes, lymphocyte transformation test, cyst formation, lymphocyte markers. Adult patients with definite or possible acute LNB (symptom duration < 6 months) should be offered a single 14-day course of antibiotic treatment. Oral doxycycline (200 mg daily) and intravenous (IV) ceftriaxone (2 g daily) are equally effective in patients with symptoms confined to the peripheral nervous system, including meningitis (level A). Patients with CNS manifestations should be treated with IV ceftriaxone (2 g daily) for 14 days and late LNB (symptom duration > 6 months) for 3 weeks (good practice points). Children should be treated as adults, except that doxycycline is contraindicated under 8 years of age (nine in some countries). If symptoms persist for more than 6 months after standard treatment, the condition is often termed post-Lyme disease syndrome (PLDS). Antibiotic therapy has no impact on PLDS (level A). 2009 EFNS

Wormser GP, Dattwyler RJ, Shapiro ED, Halperin JJ, Steere AC, Klemperer MS, et al. The clinical assessment, treatment, and prevention of Lyme disease, human granulocytic anaplasmosis, and babesiosis: clinical practice guidelines

by the Infectious Diseases Society of America. Clin Infect Dis 2006;43(9):1089-134.

Ref ID: 792

Abstract: Evidence-based guidelines for the management of patients with Lyme disease, human granulocytic anaplasmosis (formerly known as human granulocytic ehrlichiosis), and babesiosis were prepared by an expert panel of the Infectious Diseases Society of America. These updated guidelines replace the previous treatment guidelines published in 2000 (Clin Infect Dis 2000; 31[Suppl 1]:1-14). The guidelines are intended for use by health care providers who care for patients who either have these infections or may be at risk for them. For each of these Ixodes tickborne infections, information is provided about prevention, epidemiology, clinical manifestations, diagnosis, and treatment. Tables list the doses and durations of antimicrobial therapy recommended for treatment and prevention of Lyme disease and provide a partial list of therapies to be avoided. A definition of post-Lyme disease syndrome is proposed

Systematiske oversikter

Barsic B, Krajinovic V. The role of ceftriaxone in modern antimicrobial therapy - A systematic review of recent clinical trials. Infektoloski Glasnik 2002;22(4):143-51.

Ref ID: 290

Abstract: Ceftriaxone is a third generation cephalosporin, an effective antibiotic in the treatment of numerous clinical syndromes, today widely used in clinical practice. Recent data and treatment guidelines have placed ceftriaxone among the first line antibiotics for the treatment of some community-acquired infections, especially purulent meningitis, severe pneumonia, neuroborreliosis, acute otitis media and acute sinus infection. In many health care institutions, ceftriaxone is listed among reserve list of drugs, which today is quite unjustified. This paper presents a systematic review of clinical trials and treatment guidelines for certain syndromes as an evidence based need to place ceftriaxone among hospital list of drugs, exclude it from the list of reserve antibiotics and therefore make it easily available for prescribing. Also some recent studies are presented which have shown that in institutions with strict lists of reserve antibiotics resistance rate is increasing due to selective pressure of some types of antibiotics

Hansmann Y. Treatment of Lyme borreliosis secondary and tertiary stages. Medecine et Maladies Infectieuses 2007;37(7-8):479-86.

Ref ID: 659

Abstract: The treatment of secondary and tertiary Lyme borreliosis is difficult because of antibiotic lack of efficacy. This fact may be explained by several factors: the specific pathophysiology, involving not only the presence of bacteria, but also immunological reactions. There is no specific method of diagnosis resulting in difficulties for good indication of treatment and to evaluate treatment efficacy. The literature review shows that ceftriaxone and doxycycline are the two most efficient antibiotics in this indication. Even if the methodology of the published studies is not always convincing, these two antibiotics proved their efficacy in articular as well as in neurological forms of the disease. In the late stage of borreliosis, antibiotics are less efficient. Various treatment modalities with different dosage or duration of treatment cannot let us conclude on a convincing regimen. [References: 60]

Ljostad U, Mygland A. Lyme borreliosis in adults. *Tidsskr Nor Laegeforen* 2008;128(10):1175-8.

Ref ID: 655

Abstract: **BACKGROUND:** Lyme borreliosis is a MULTISYSTEM: tick-borne infection caused by the spirochete *Borrelia burgdorferi*. We present a survey of clinical stages, diagnosis, treatment and prognosis of Lyme borreliosis in adults. **MATERIAL AND METHODS:** The article is based on literature retrieved through database searches and own experience. **RESULTS AND INTERPRETATION:** In Norway, Lyme borreliosis is most prevalent in coastal areas from the south and up to Trondelag. Lyme disease can be classified into three stages; localised stage, and early and late disseminated stages. A laboratory gold standard does not exist, so the diagnosis is based on a combination of clinical manifestations and indirect detection of the bacteria, most often specific antibodies. Antibody results must be interpreted with caution. No medication is needed after a tick bite, but all manifestations of Lyme borreliosis should be treated with antibiotics according to guidelines. The prognosis is generally good. Post Lyme disease with persistent symptoms after borreliosis is a controversial condition. No studies have demonstrated persistent infection with borrelia bacteria in patients with chronic complaints after adequate antibiotic treatment, and additional antibiotic treatment does not improve quality of life in these patients

Ljostad U, Henriksen TH. Management of neuroborreliosis in European adult patients. *Acta Neurol Scand* 2008;Supplementum. 188:22-8.

Ref ID: 103

Abstract: **OBJECTIVES:** To survey present knowledge and controversies in European neuroborreliosis. **Material and METHODS:** The article is based on available literature, own experience, and a speech held by the authors. together on the Norwegian annual neurological meeting. **RESULTS:** Diagnosis of neuroborreliosis is based on clinical neurological findings, laboratory support of borrelia infection, and indications of causality between neurological findings and borreliosis. In the absence of means to identify *B. burgdorferi*, antibody tests are used for laboratory diagnosis. Two to three weeks courses of IV penicillin or ceftriaxone are highly effective in neuroborreliosis. Oral doxycyclin is probably equally effective. Remaining symptoms five years after treatment for neuroborreliosis are reported in 25-50% of patients. **CONCLUSIONS:** We suggest two levels of diagnostic accuracy; definite and possible neuroborreliosis. These case definitions are proposed to make the basis for treatment decisions. The prognosis of neuroborreliosis and pathophysiology of post-treatment conditions need further studies. Extensive treatments with antibiotics are not recommended

Mohseni ZM. Treatment and follow up of disseminated and late Lyme disease. *Medecine et Maladies Infectieuses* 2007;37(7-8):368-80.

Ref ID: 135

Abstract: The aim of this review was to analyze the current strategies of treatment and follow-up of disseminated and late Lyme borreliosis. A comprehensive search was performed using the Medline database. Only relevant reviews, expert guidelines and randomized controlled clinical trials were selected and, if necessary, open trials. Major drugs used in these studies were amoxicillin, doxycycline, penicillin G, and ceftriaxone. Oral administration of antibiotics was preferred in Lyme arthritis whereas parenteral drugs were mostly used in neuroborreliosis. The treatment duration usually ranged from 14 to 30 days. Prolonged antibiotic courses recommended by some authors in post-Lyme syndromes were not validated by several randomized placebo controlled studies. Follow up patterns were analyzed in order to determine possible prognosis

parameters allowing to distinguish active *Borrelia burgdorferi* infection from a sequel of infection

Randomiserte kontrollerte studier

Dattwyler RJ, Wormser GP, Rush TJ, Finkel MF, Schoen RT, Grunwaldt E, et al. A comparison of two treatment regimens of ceftriaxone in late Lyme disease. *Wien Klin Wochenschr* 2005;117(11-12):393-7.

Ref ID: 671

Abstract: **BACKGROUND:** The optimal duration of treatment for patients with late Lyme disease is unresolved. **METHODS:** In a prospective, open label, randomized, multi-center study, a 14 day course of ceftriaxone was compared to 28 days of therapy. Entry criteria included objective abnormalities compatible with late Lyme disease and serologic reactivity to *Borrelia burgdorferi*. Randomization took place prior to obtaining serologic results. Clinical response was rated as cure; improvement; failure; or not assessable. **RESULTS:** Of the 201 patients randomized, 21 patients in the 14 day group and 37 in the 28-day group were excluded from the study for failure to meet serologic criteria. Of those who met serologic criteria, 80 patients received 14 days and 63 received 28 days of ceftriaxone. At time of last evaluation, there were 5 treatment failures in the 14 day group and none in the 28 day group ($p = 0.07$). Clinical cure rates were 76% for the 14 day group and 70% for the 28 day group ($p = \text{NS}$). Therapy was discontinued due to adverse events for a significantly greater proportion of patients in the 28-day group compared to the 14-day group ($p < 0.02$). **CONCLUSIONS:** Ceftriaxone for 14 days eradicated the signs and symptoms of late Lyme disease in the majority of evaluable patients. Although there were more failures in the 14-day group than in the 28-day group, this study did not have the power to determine if a clinical subset of patients may benefit from 28 days of therapy

- . Karlsson M, Hammers-Berggren S, Lindquist L, Stiernstedt G, Svenungsson B. Comparison of intravenous penicillin G and oral doxycycline for treatment of Lyme neuroborreliosis. *Neurology* 1994;44(7):1203-7.

Ref ID: 486

Abstract: To compare the efficacy of oral doxycycline and IV penicillin G for the treatment of neuroborreliosis, we randomized consecutive patients with Lyme neuroborreliosis to receive either IV penicillin G (3 g q 6 h) or oral doxycycline (200 mg q 24 h) for 14 days. All patients had antibodies against *Borrelia burgdorferi* in serum, CSF, or both, or had a positive CSF culture. Twenty-three patients randomized to penicillin G and 31 patients to doxycycline were included in the study. All patients improved during treatment, and there were no significant differences between the two treatment groups in patient scoring, CSF analysis, or serologic and clinical follow-up during 1 year. There were no treatment failures, although one patient in each treatment group was re-treated because of residual symptoms. In conclusion, oral doxycycline is an adequate and cost-effective alternative to IV penicillin for the treatment of Lyme neuroborreliosis

- . Karlsson M, Hammers S, Nilsson-Ehle I, Malmberg A-S, Wretling B. Concentrations of doxycycline and penicillin G in sera and cerebrospinal fluid of patients treated for neuroborreliosis. *Antimicrob Agents Chemother* 1996;40(5):1104-7.

Ref ID: 445

Abstract: Concentrations of doxycycline and penicillin G in serum and cerebrospinal fluid (CSF) were analyzed in 46 patients during treatment for neuroborreliosis. Twenty patients were treated intravenously with penicillin G at 3 g every 6 h (q6h), and 26 patients were treated orally with doxycycline at 200 mg q24h. All samples were collected on day 13 of treatment. The median concentrations of penicillin G in serum were 0.5, 37, and 5.6 mug/ml before and 1 and 3 h after drug administration, and that in CSF was 0.5 (range, 0.3 to 1.6) mug/ml after 2 to 3 h. The median concentrations of doxycycline in serum were 2.1, 6.1, and 4.7 mug/ml before and 2 and 6 h after drug administration, and that in CSF was 0.6 (range, 0.4 to 2.5) mug/ml after 4 h. All patients had concentrations of penicillin G or doxycycline in CSF above the lowest reported MICs of penicillin G (0.003 mug/ml) and doxycycline (0.12 mug/ml) for *Borrelia burgdorferi*. However, no patients had a drug concentration in CSF above the highest reported MIC of penicillin G (8 mug/ml), and only one had a drug concentration in CSF above the highest reported MIC of doxycycline (2 mug/ml), despite good clinical response to treatment. No treatment failure or relapse was observed during a 1-year follow-up, although one patient treated with penicillin G and one treated with doxycycline were retreated because of residual pain. The chosen dosages of penicillin G and doxycycline seem to give sufficient concentrations in serum and CSF for the treatment of neuroborreliosis

- . Ljostad U, Skogvoll E, Eikeland R, Midgard R, Skarpaas T, Berg A, et al. Oral doxycycline versus intravenous ceftriaxone for European Lyme neuroborreliosis: a multicentre, non-inferiority, double-blind, randomised trial. *The Lancet Neurology* 2008;7(8):690-5.

Ref ID: 118

Abstract: Background: Use of intravenous penicillin and ceftriaxone to treat Lyme neuroborreliosis is well documented, although oral doxycycline could be a cost-effective alternative. We aimed to compare the efficacy of oral doxycycline with intravenous ceftriaxone for the treatment of Lyme neuroborreliosis. Methods: From April, 2004, to October, 2007, we recruited consecutive adult patients from nine hospitals in southern Norway into a non-inferiority trial. Inclusion criteria were neurological symptoms suggestive of Lyme neuroborreliosis without other obvious causes, and presence of any of the following: a CSF white-cell count of more than five per mL; intrathecal production of specific *Borrelia burgdorferi* antibodies; or acrodermatitis chronicum atrophicum. Patients were randomly allocated to receive 200 mg oral doxycycline or 2 g intravenous ceftriaxone once per day for 14 days, in a double-blind, double-dummy design. A composite clinical score (range 0 to 64, 0=best) was based on standardised interviews and clinical neurological examination. The primary outcome was reduction in clinical score at 4 months after the start of treatment. Analysis was per protocol. This trial is registered with ClinicalTrials.gov, number NCT00138801. Findings: Of 118 patients who underwent randomisation, 102 completed the study (mean clinical score at baseline 85 [SD 41]). 4 months after the start of treatment, mean score improvement in the doxycycline group (n=54) was 45 (95% CI 36 to 55) points and that in the ceftriaxone group (n=48) was 44 (34 to 54) points (95% CI for difference between groups -09 to 11; p=084). 26 (48%) patients in the doxycycline group and 16 (33%) in the ceftriaxone group had total recovery (95% CI for difference between groups -4% to 34%; p=013). Side-effects possibly related to treatment were reported in 21 (37%) and 26 (46%) patients in these groups, respectively (-28% to 9%; p=030). Three patients discontinued ceftriaxone treatment owing to adverse events. Interpretation: Oral doxycycline is as efficient as intravenous ceftriaxone for the treatment of European adults with Lyme neuroborreliosis. Funding: Sorlandet Kompetansefond. 2008 Elsevier Ltd. All rights reserved

- . Ogrinc K, Logar M, Lotric-Furlan S, Cerar D, Ruzic-Sabljić E, Strle F. Doxycycline versus ceftriaxone for the treatment of patients with chronic Lyme borreliosis. *Wien Klin Wochenschr* 2006;118(21-22):696-701.

Ref ID: 175

Abstract: Background: Therapeutic guidelines for treatment of late manifestations of Lyme borreliosis have not yet become well established. Patients with symptoms suggesting central nervous system involvement are often treated with courses of intravenous ceftriaxone. This is an expensive treatment approach with potentially severe side effects. We compared the efficacy, side effects and costs of doxycycline and ceftriaxone in the treatment of such patients. Patients and methods: Adult patients qualified for the study if they had had nonspecific symptoms suggesting central nervous system involvement for more than six months (but without overt clinical signs of the involvement), had positive serum borrelial antibody titers and/or erythema migrans prior to the onset of symptoms, had not been previously treated with antibiotics and did not have pleocytosis in the cerebrospinal fluid. Patients were given either 100 mg of oral doxycycline twice daily for 4 weeks (23 patients) or 2 g of intravenous ceftriaxone daily for 2 weeks followed by 100 mg of doxycycline twice daily for another 2 weeks (23 patients). Clinical outcome was assessed during a 12-month follow-up period. Results: Improvement in the frequency and/or the intensity of symptoms was reported by more than two-thirds of the 46 patients enrolled in the study. The two treatment regimens were found to be correspondingly effective. Photosensitivity reactions and gastrointestinal symptoms were noted more often among patients receiving doxycycline than in those receiving ceftriaxone. Treatment with doxycycline proved to be much cheaper than with ceftriaxone. Conclusions: In patients with previously untreated chronic Lyme borreliosis with symptoms suggesting central nervous system involvement but without overt clinical signs of it, and without pleocytosis in the cerebrospinal fluid, treatment with doxycycline is as effective as with ceftriaxone. Treatment with doxycycline is cheap and relatively safe, but gastrointestinal symptoms and photosensitivity reactions can be expected more often than with ceftriaxone. Springer-Verlag 2006

- . Pfister H-W, Preac-Mursic V, Wilske B, Einhaupl KM. Cefotaxime vs penicillin G for acute neurologic manifestations in Lyme borreliosis. A prospective randomized study. *Arch Neurol* 1989;46(11):1190-4.

Ref ID: 579

Abstract: We randomly assigned 21 patients with painful Lyme neuroborreliosis radiculitis (Bannwarth's syndrome) and neuroborreliosis meningitis to a 10-day treatment with either penicillin G, 4 x 5 million U/d (n = 10) or cefotaxime sodium, 3 x 2 g/d (n = 11), intravenously. We were not able to demonstrate clinical differences between groups, either during the 10-day treatment period or at follow-up examination a mean of 7.7 months after antibiotic therapy. Cerebrospinal fluid cefotaxime concentrations reached the minimum inhibitory concentration at the 90% level for *Borrelia burgdorferi* in all patients, while none of the patients treated with penicillin G had cerebrospinal fluid concentrations above the minimum inhibitory concentration at the 90% value. We conclude that patients with acute neurologic manifestations of Lyme borreliosis may benefit from a 10-day treatment with cefotaxime or penicillin G. Cerebrospinal fluid antibiotic concentrations above the minimum inhibitory concentration at the 90% value, as observed in all patients treated with cefotaxime, offer the most hope for long-term prognosis

- . Pfister H-W, Preac-Mursic V, Wilske B, Schielke E, Sorgel F, Einhaupl KM. Randomized comparison of ceftriaxone and cefotaxime in Lyme neuroborreliosis. *J Infect Dis* 1991;163(2):311-8.

Ref ID: 559

Abstract: In this prospective, randomized, open trial, 33 patients with Lyme neuroborreliosis were assigned to a 10-day treatment with either ceftriaxone, 2 g intravenously (iv) every 24 h (n = 17), or cefotaxime, 2 g iv every 8 h (n = 16). Of the 33 patients, 30 were eligible for analysis of therapeutic efficacy. Neurologic symptoms improved or even subsided in 14 patients of the cefotaxime group and in 12 patients of the ceftriaxone group during the treatment period. At follow-up examinations after a mean of 8.1 months, 17 of 27 patients examined were clinically asymptomatic. In one patient *Borrelia burgdorferi* was isolated from the cerebrospinal fluid (CSF) 7.5 months after ceftriaxone therapy. CSF antibiotic concentrations were above the MIC 90 level for *B. burgdorferi* in nearly all patients examined. Patients with Lyme neuroborreliosis may benefit from a 10-day treatment with ceftriaxone or cefotaxime. However, as 10 patients were symptomatic at follow-up and borreliae persisted in the CSF of one patient, a prolongation of therapy may be necessary

Ukjent artikkeltype

Erbguth F. Treatment of neuroborreliosis. *Nervenheilkunde* 1989;8(6):293-6.

Ref ID: 589

Kolmel HW, Lange R. Neuroborreliosis. Symptomatology, diagnosis and therapy. *Z Arztl Fortbild (Jena)* 1994;88(1):11-6.

Ref ID: 495

Segura PF, Fernandez MM. Treatment of borreliosis. *Enferm Infecc Microbiol Clin* 1998;16(5):239-44.

Ref ID: 720

Selby G, Bridges SJ, Hanington L. Should Lyme disease affecting the nervous system be treated with oral or intravenous antibiotics? *Archives of Disease in Childhood Education and Practice* 2008;dis.(4):132-4.

Ref ID: 651

- . Steurer J. Oral doxycycline versus intravenous ceftriaxone for the treatment of European neuroborreliosis. *Schweizerische Rundschau für Medizin - Praxis* 2009;98(16):909-10.

Ref ID: 36

Elektroniske kliniske oppslagsverk

Clinical Evidence:

Lyme disease:

<http://clinicalevidence.bmj.com/ceweb/conditions/ind/0910/0910.jsp>

UpToDate

Treatment of Lyme disease

http://www.uptodate.com/contents/nervous-system-lyme-disease?source=search_result&selectedTitle=6%7E12

Bell's palsy: Prognosis and treatment

http://www.uptodate.com/contents/bells-palsy-prognosis-and-treatment?source=search_result&selectedTitle=11%7E12

Vedlegg

Søkestrategier

Database: EMBASE 1980 to 2011 Week 06, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1948 to Present

Dato: 16.02.2011

Filter: Ingen

Treff: 764 treff

- 1 Lyme Neuroborreliosis/
- 2 exp Lyme Disease/
- 3 Chronic Disease/
- 4 2 and 3
- 5 ((lyme adj3 (chronic* or polyradicul* or meningo* or monon* or encephalo* or neuroborrel* or nervous*)) or neuroborrelio*).tw.
- 6 1 or 4 or 5
- 7 exp Anti-Bacterial Agents/
- 8 Anti-Infective Agents/
- 9 (antibiotic* or ((antiinfective or anti-infective or anti-bacterial or antibacterial) adj agent*).tw.
- 10 (antimicrobial or anti-microbial).tw.
- 11 7 or 8 or 9 or 10
- 12 6 and 11
- 13 12 use prnz
- 14 ((lyme adj3 (chronic* or polyradicul* or meningo* or monon* or encephalo* or neuroborrel* or nervous*)) or neuroborrelio*).tw.
- 15 exp antibiotic agent/
- 16 antiinfective agent/
- 17 (antibiotic* or ((antiinfective or anti-infective or anti-bacterial or antibacterial) adj agent*).tw.
- 18 (antimicrobial or anti-microbial).tw.
- 19 or/15-18
- 20 14 and 19
- 21 20 use emez

- 22 13 or 21
- 23 remove duplicates from 22

Database: Cochrane

Dato: 16.02.2011

Filter: Ingen

Treff: 23

- #1 MeSH descriptor Lyme Neuroborreliosis explode all trees
- #2 MeSH descriptor Lyme Disease explode all trees
- #3 MeSH descriptor Chronic Disease explode all trees
- #4 (#2 AND #3)
- #5 ((lyme NEAR/3 (chronic* or polyradicul* or meningo* or monon* or encephalo* or neuroborrel* or nervous*)) or neuroborrelio*):ti,ab,kw
- #6 (#1 OR #4 OR #5)
- #7 MeSH descriptor Anti-Bacterial Agents explode all trees
- #8 MeSH descriptor Anti-Infective Agents, this term only
- #9 (antibiotic* or ((antiinfective or anti-infective or anti-bacterial or antibacterial) NEXT agent*)):ti,ab,kw
- #10 (antimicrobial* or anti-microbial*)
- #11 (#7 OR #8 OR #9 OR #10)
- #12 (#6 AND #11)
- #13 (#6 AND NOT #12)

Database: CRD

Dato: 16.02.2011

Filter: Ingen

Treff: 4

- #1 MeSH Lyme Neuroborreliosis EXPLODE 1 2 3 4 5
- #2 MeSH Lyme Disease EXPLODE 1 2 3
- #3 MeSH Chronic Disease EXPLODE 1
- #4 #2 and #3
- #5 (lyme NEAR chronic*) OR (lyme NEAR polyradicul*) OR (lyme NEAR meningo*)
OR (lyme NEAR monon*)
- #6 (lyme NEAR encephalo*) OR (lyme NEAR neuroborrel*) OR (lyme NEAR nervous*)
OR neuroborrelio*
- #7 #1 or #4 or #5 or #6
- #8 MeSH Anti-Bacterial Agents EXPLODE 1
- #9 MeSH Anti-Infective Agents

#10 antibiotic*

#11 (antimicrobial* NEAR agent*) OR (anti-microbial* NEAR agent*) OR (antiinfective* NEAR agent*)

#12 (anti-infective* NEAR agent*) OR (anti-bacterial* NEAR agent*) OR (antibacterial* NEAR agent*)

#13 #8 or #9 or #10 or #11 or #12

#14 #7 and #13

Database: Best Practice

Dato: 16.02.2011

Filter: Ingen

Treff: 1

Søk: "Lyme neuroborreliosis" eller "Neuroborreliosis" gir begge henvisning til Lyme Disease i Clinical Evidence.

Database: Clinical Evidence

Dato: 16.02.2011

Filter: Ingen

Treff: 1

Søk: "Lyme Neuroborreliosis" gav treff på Lyme Disease, men underpunkter om neuroborreliosis:

Lyme disease:

<http://clinicalevidence.bmj.com/ceweb/conditions/ind/0910/0910.jsp>

Database: UpToDate

Dato: 16.02.2011

Filter: Ingen

Treff: 12

Søk på "Lyme neuroborreliosis" eller "Neuroborreliosis" ga følgende treff:

Clinical manifestations of Lyme disease in adults

Treatment of Lyme disease

Diagnosis of Lyme disease

Lyme disease: Clinical manifestations in children

Pathophysiology, clinical features, and diagnosis of spontaneous low cerebrospinal fluid pressure headache

Nervous system Lyme disease
Facial nerve palsy in children
Clinical features and management of relapsing fever
Bell's palsy: Pathogenesis, clinical features, and diagnosis
Lyme carditis
Bell's palsy: Prognosis and treatment
Microbiology, pathogenesis, and epidemiology of relapsing fever

Database: National Guidelines Clearinghouse

Dato: 17.02.2011

Filter: Ingen

Treff: 2

Søk: Neuroborreliosis

Halperin JJ, Shapiro ED, Logigian E, Belman AL, Dotevall L, Wormser GP, Krupp L, Gronseth G, Bever CT Jr. Practice parameter: treatment of nervous system Lyme disease (an evidence-based review). Report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology* 2007 Jul 3;69:1-12.

Wormser GP, Dattwyler RJ, Shapiro ED, Halperin JJ, Steere AC, Klemmner MS, Krause PJ, Bakken JS, Strle F, Stanek G, Bockenstedt L, Fish D, Dumler JS, Nadelman RB. The clinical assessment, treatment, and prevention of lyme disease, human granulocytic anaplasmosis, and babesiosis: clinical practice guidelines by the Infectious Diseases Society of America. *Clin Infect Dis* 2006 Nov 1;43(9):1089-134

Database: TRIP+

Dato: 17.02.2011

Filter: Ingen

Treff: 41

Søk: Neuroborreliosis

Database: G-I-N

Dato: 17.02.2011

Filter: Ingen

Treff: 0

Søk: Neuroborreliosis

Database: NHS Evidence - National Library of Guidelines

Dato: 17.02.2011

Filter: Ingen

Treff: 0

Søk: Neuroborreliosis