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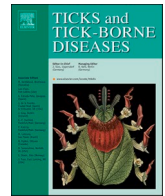
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Original article

Antibiotic therapy of neuroborreliosis: A survey among infectious disease specialists and neurologists in Norway, Sweden, and Denmark

Emilie Bernardshaw^{a,†}, Rosa M.M. Gyntheren^{a,†,*}, Daniel Bremell^{b,c}, Helene Mens^a, Christian Stenør^{d,e}, Åslaug R. Lorentzen^{f,g}, Jacob Bodilsen^h, Randi Eikeland^{f,i}, Anne-Mette Lebech^{a,e,*}

^a Department of Infectious Diseases, Copenhagen University Hospital, Rigshospitalet, Blegdamsvej 9, Rigshospitalet, Copenhagen 2100, Denmark

^b Department of Infectious Diseases, Region Västra Götaland, Sahlgrenska University Hospital, Gothenburg, Sweden

^c Department of Infectious Diseases, Institute of Biomedicine, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden

^d Department of Neurology, University hospital-Herlev Hospital, Copenhagen, Denmark

^e Department of Clinical Medicine, Faculty of Health and Medical Sciences, University of Copenhagen, Denmark

^f Department of Neurology, Sorlandet Hospital Trust, Kristiansand, Norway

^g The Norwegian National Advisory Unit on Tick-borne Diseases, Sorlandet Hospital Trust, Kristiansand, Norway

^h Department of Infectious Diseases, Aalborg University Hospital, Aalborg, Denmark

ⁱ The Faculty of health and sport sciences, University of Agder, Grimstad, Norway

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ABSTRACT

Introduction: Neuroborreliosis (NB) is a prevalent tick-borne neuroinfection in Europe. To delineate current practice in antimicrobial management of adults with NB and to prioritize future trials needed to optimize treatment recommendations, a questionnaire-based survey was performed.

Methods: A self-administered Internet-based survey of NB treatment practices among specialists in infectious diseases and neurology based in Norway, Sweden, and Denmark was carried out between October 2021 and February 2022. The participants were also asked to prioritize four pre-defined research questions for randomized controlled trials (RCTs) on therapy for NB.

Results: In total, 290 physicians (45% female) from Norway (30%), Sweden (40%), and Denmark (30%) participated in the survey. Of the responders, 230 (79%) were infectious disease specialists and 56 (19%) were neurologists.

The preferred antibiotic treatment for patients with early NB was oral doxycycline ($n = 225$, 78%). Intravenous (IV) penicillin, ceftriaxone, or cefotaxime for the full treatment course was favored by 12%. A preferred treatment duration of 10–14 days for patients with NB was reported by 245 respondents (85%), most common among participants from Sweden (97%).

A total of 170 (59%) responders reported having local hospital guidelines on the treatment of NB, most often with recommendation of oral doxycycline (92%) for 10–14 days (90%) as first line treatment.

The prioritization score for future RCTs was highest for adjunctive prednisone therapy in NB patients with facial palsy (median 5; IQR 4–6) and for placebo versus repeated antibiotics in patients with persistent symptoms after completed antibiotic therapy for NB (median 5, IQR 3–6).

Conclusion: In Sweden, all respondents preferred treating NB with oral doxycycline for 10–14 days, whereas 5% in Norway and 19% in Denmark still treat NB with IV antibiotics for the entire treatment course. RCTs to define the role of adjunctive prednisolone in NB patients with facial palsy and repeated antibiotics in patients with persistent symptoms are prioritized for future research.

* Corresponding authors.

E-mail addresses: rosa.maja.moehring.gyntheren.01@regionh.dk (R.M.M. Gyntheren), anne-mette.lebech@regionh.dk (A.-M. Lebech).

† The authors contributed equally to the publication

1. Introduction

Neuroborreliosis (NB) is a tick-borne infection caused by spirochetes of the *Borrelia burgdorferi* sensu lato (s.l.) complex (Stanek et al., 2012) and in Europe, NB is among the most prevalent bacterial infections of the nervous system. Since 2018, NB has been included on the list of diseases under the surveillance of the European Centre for Disease Prevention and Control (ECDC) (Lancet, 2018).

Most European physicians agree on the diagnostic criteria for NB presented by the European Federation of Neurological Society (EFNS) (Mygland et al., 2010). Three diagnostic criteria must be fulfilled to diagnose definite NB: (I) neurological symptoms suggestive of NB (with other causes excluded); (II) Cerebrospinal fluid (CSF) pleocytosis; (III) *Borrelia burgdorferi*-specific antibodies in CSF (produced intrathecally). If two out of three criteria are fulfilled, the diagnosis possible NB is assigned. Early NB is defined as neurological symptoms for < 6 months either from the peripheral nervous system (PNS) or the central nervous system (CNS). Late NB as neurological symptoms from the CNS or PNS for > 6 months (Mygland et al., 2010).

In Europe, several recommendations are available regarding therapy for NB (Albåge et al., 2009; Dessau et al., 2014; Helsedirektoratet, 2022; Lantos et al., 2021; Mygland et al., 2010; NICE, 2018; Rauer et al., 2020). Especially route of antibiotic administration, treatment duration as well as the benefit of additional antibiotics in patients with residual symptoms after NB remains an area of controversy. In Sweden, Norway, and Denmark a high degree of accordance with the NB treatment guidelines is seen.

For healthcare professionals, inconsistency between guidelines may lead to uncertainty or confusion among clinicians when choosing antibiotic therapy for treatment of NB. Thus, discrepancy between recommendations and everyday treatment practice of NB patients has been reported in several countries e.g. Norway, Belgium, and Denmark, regarding intravenous (IV) antibiotic therapy versus oral antibiotic administration (L. Geebelen, 2019; Lorentzen Å et al., 2017; Nordberg et al., 2020).

A better understanding of everyday management of patients with NB is crucial for understanding practice variation and educational purposes as well as for describing areas of scientific uncertainty.

In the present study, we aimed to delineate current practice in antimicrobial management of adult patients with NB and to prioritize future trials needed to optimize treatment recommendations. Therefore, we performed a questionnaire-based survey among infectious disease specialists and neurologists in Norway, Sweden, and Denmark.

2. Materials and methods

2.1. Development of the survey

A self-administered Internet-based questionnaire-based survey of NB treatment practices among specialists in infectious diseases and neurology based in Norway, Sweden, and Denmark was carried out between October 2021 and February 2022 (Supplementary Material). The questionnaire was developed specifically for this study using the REDCap electronic research data research tool (Harris et al., 2009; Harris et al., 2019). The survey was drafted by two infectious disease physicians from Copenhagen University Hospital, Rigshospitalet, Denmark, followed by a critical review by physicians from both Norway and Sweden. The questionnaire was tested in a focus group of infectious disease physicians at Rigshospitalet, Copenhagen, after which it was finalized.

2.2. Questionnaire

The questionnaire included demographic data of the respondents such as country of residence, sex, age, experience as a specialist, hospital characteristics (departments present on-site), and an estimate of number

of patients with NB treated per year. Respondents were asked about their preferred antimicrobial regimen for NB treatment, duration of treatment, and whether they have a local and/or a national guideline for treatment of patients with NB. Finally, the participants were asked to prioritize four pre-defined research questions for randomized controlled trials (RCTs) on therapy for NB (6 = high priority, 1 = low priority). The research questions for RCTs to prioritize were: (1) To examine if adjunctive prednisolone therapy to antibiotic therapy can reduce the severity of sequelae in NB patients with facial palsy; (2) Studies of placebo vs. repeated antibiotics in patients with persistent symptoms 6 months after completed antibiotic therapy for NB in order to examine effect on clinical outcome; (3) Studies comparing duration of antibiotic therapy in NB to evaluate efficiency of treatment e.g. 2 and 4 weeks of antibiotic courses and (4) Comparative trials of antimicrobial treatment regimens for NB in order to evaluate the efficacy of oral antibiotics in comparison to IV antibiotics in the treatment of NB.

2.3. Distribution

The survey was sent by e-mail to departments of infectious diseases at Norwegian, Swedish, and Danish hospitals, as well as neurological departments in Norway and Denmark. In Denmark, a reminder was sent by e-mail two weeks before the closure of the survey. Due to the workload during the COVID-19 pandemic, this was not done in Sweden and Norway.

2.4. Statistical analyses

Categorical and binary variables were presented as frequencies and percentages. Continuous variables were shown as medians with inter-quartile ranges (IQR). Graphs were made in GraphPad Prism version 9.3.1 (GraphPad Software, San Diego, CA, USA).

2.5. Ethical considerations

Participation in the survey was voluntary and completely anonymous. Approval from an ethical committee was not required for this type of study in the participating countries.

3. Results

3.1. Characteristics of respondents

In total, 290 physicians (45% female) participated in the survey of which 230 (79%) were infectious disease specialists and 56 (19%) were neurologists (Table 1). A total of 87 (30%) respondents were Norwegian, 115 (40%) were Swedish, and 88 (30%) were Danish.

The majority of study participants ($n = 249$, 87%) worked at hospitals with an on-site department of infectious diseases. In total, 130 (45%) respondents worked at hospitals where 11–25 patients with NB were treated per year and 50 (17%) reported that their hospital treated 26–50 patients per year.

3.2. Preferred antimicrobial regimens

The preferred antimicrobial regimen for treating early NB patients was oral doxycycline 100 mg or 200 mg b.i.d. ($n = 225$, 78%) (Table 2). Three respondents preferred doxycycline 200 mg o.d. Divided in specialties, 77% ($n = 176$) of the ID specialists and 82% ($n = 45$) of the neurologists favored doxycycline for NB treatment (data not shown). All the Swedish respondents preferred doxycycline ($n = 114$, 99%), while two thirds of the Norwegian ($n = 61$, 70%) and Danish ($n = 54$, 61%) respondents preferred doxycycline (Fig. 1). A full treatment duration with IV antibiotics was favored by 36 (12%) of the respondents (ceftriaxone, penicillin or cefotaxime).

For treatment of early NB, 213 (74%) study participants considered

Table 1
Characteristics of respondents.

	Total respondents N = 290	Percentage%
Sex		
Female	129	44.5
Country		
Norway	87	30.0
Sweden	115	39.7
Denmark	88	30.3
Age (years)		
≤ 34	15	5.2
35–44	106	36.6
≥ 45	169	58.3
Experience as a medical doctor		
< 5 years	11	3.8
5–14 years	73	25.3
15–24 years	107	37.0
≥ 25 years	98	33.9
Medical Specialty		
Infectious diseases	230	79.3
Neurology	56	19.3
Departments present at the participant's workplace		
Department of Infectious Diseases	249	85.9
Department of Neurology	163	56.2
Number of patients with NB treated per year		
≤ 10	65	22.4
11–25	130	44.8
26–50	50	17.2
≥ 50	16	5.5
Don't know	29	10.0
Complete response	290	100.0

Abbreviations: NB, Lyme neuroborreliosis.

Table 2
Preferred antibiotic regimens for treatment of NB among respondents.

	Total respondents N = 290	Percentage %
Antimicrobial treatment of early NB		
Oral Doxycycline	225	77.6
a) 100 mg b.i.d. (eventually 1st day 200 mg b.i.d.)		
b) 200 mg b.i.d.		
IV Ceftriaxone 2 g q.d.	30	10.3
IV Penicillin/Ceftriaxone and shift to oral Doxycycline	20	6.9
IV Penicillin G 5 MIE q.i.d.	4	1.4
IV Cefotaxime 2 g t.i.d.	2	0.7
Other	7	2.4
Don't know	2	0.7
NB patients where IV antibiotic therapy is preferred		
Patients with severe radicular pains	66	22.8
Patients with long duration of symptoms (> 6 months)	53	18.3
Patients with cranial nerve palsy	34	11.7
Other group of patients	60	20.7
No specific group	78	26.9
Never treat with IV antibiotics	40	13.8
Don't know	16	5.5

Abbreviations: N, number of respondents; NB, Lyme neuroborreliosis; q.d, quaque die, once per day; b.i.d, bis in die, twice per day; t.i.d., ter in die, three times per day; q.i.d., quarter in die, four times per day; IV, intravenous.

oral doxycycline and IV antibiotic treatment equally effective, while 24 (8%) found IV antibiotics superior to doxycycline (data not shown). IV antibiotic treatment was favored in patients with severe radicular pains ($n = 66$, 23%), patients with long duration of symptoms prior to diagnosis ($n = 53$, 19%), and patients with cranial nerve palsy ($n = 34$, 12%).

The preferred treatment duration of antimicrobials for patients with early NB was 10–14 days (85%) (Fig. 2). When looking at the ID specialists and neurologists separately, 83% ($n = 190$) ID specialists and 91% ($n = 51$) neurologists preferred this treatment duration. Early and

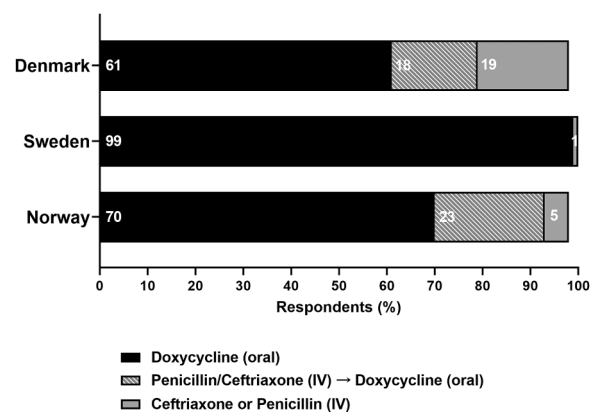


Fig. 1. Choice of antimicrobial therapy in early neuroborreliosis among 290 infectious disease specialists and neurologists in Norway, Sweden, and Denmark.

Abbreviations: n, number; IV, intravenous.

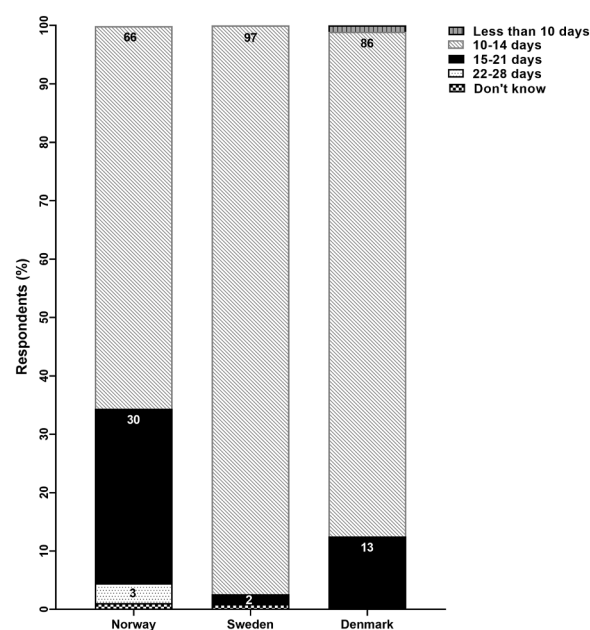


Fig. 2. Duration of treatment with antimicrobials for early neuroborreliosis among 290 infectious disease specialists and neurologists in Norway, Sweden, and Denmark.

late NB were treated differently by 26% ($n = 74$) of the physicians. Differences in treatment included extending the duration to 3–4 weeks, as well as a tendency towards the use of IV antibiotics in patients with late NB (data not shown).

National guidelines exist in all three participating countries (Albåge et al., 2009; Dessau et al., 2014; Helsedirektoratet, 2022). According to 59% ($n = 170$) of the physicians, local hospital guidelines on treatment of NB were present and most reported recommendation of oral doxycycline as first line treatment for early NB in their guideline ($n = 156$, 92%), with a duration of 10–14 days ($n = 227$, 90%).

3.3. Prioritization of future RCTs

Future RCTs on the use of adjunctive prednisolone therapy (median 5, IQR 4–6) and comparison of antibiotics versus placebo in patients with persistent symptoms after antimicrobial therapy for NB (median 5, IQR 3–6) had the highest priority among the respondents (Table 3). Studies on the duration of antibiotic therapy (median 4, IQR 3–5) and

Table 3

Prioritization scores in future randomized controlled trials on treatment of Lyme neuroborreliosis.

	Total participants (N = 290) n/N	Prioritization score (6 = high priority, 1 = low priority) Median (IQR)
Use of adjunctive prednisone therapy, especially in patients with facial palsy	270/287	5 (4–6)
Placebo vs. antibiotics in patients with persistent symptoms 6 months after completed antibiotic therapy	269/289	5 (3–6)
Duration of antibiotic therapy*	273/288	4 (3–5)
Comparative trials of antimicrobial treatments	267/288	4 (3–5)

Abbreviations: n, number of respondents; N, total count; IQR, interquartile range; NB, Lyme neuroborreliosis; IV, intravenous.

* E.g., two weeks versus four weeks of antibiotic therapy.

comparison of different antimicrobial treatments (median 4, IQR 3–5) were assigned moderate scores.

Several study participants stated that their reason for assigning research questions lower scores was that reliable data from similar trials already existed.

4. Discussion

In this survey among 290 neurologists and specialists in infectious diseases in Norway, Sweden, and Denmark, the preferred antimicrobial regimen in patients with NB was oral doxycycline (78%) for a treatment duration of 10–14 days (84%).

For future RCTs on NB treatment, high prioritization scores were given to studies investigating if adjunctive oral prednisolone therapy to antibiotic therapy can reduce the severity of sequelae in NB patients with facial palsy. In addition, studies to examine the effect on clinical outcome of repeated antibiotics compared to placebo in patients with persistent symptoms after completed antibiotic therapy for NB were highly rated. Thus, indicating clinical uncertainty regarding these questions.

4.1. Preferred antibiotic regimens

In 2009, the EFNS guidelines recommended the use of oral doxycycline or IV ceftriaxone for treatment of NB, stating equal efficiency between the two treatments (Mygland et al., 2010). The National guidelines (Albåge et al., 2009; Helsedirektoratet, 2022; Lebech et al., 2021) of Norway, Sweden, and Denmark are in correspondence with the EFNS recommendations, which presumably contribute to the high inclination to treat NB patients with oral doxycycline in all countries. For NB patients with involvement of the CNS, Norwegian national guidelines from 2022 recommend considering treatment initiation with IV antibiotics, followed by oral doxycycline (Helsedirektoratet, 2022). Oral doxycycline for the entire treatment duration of patients with NB was first introduced in the Danish national guidelines in 2021 (Lebech et al., 2021) whereas the Swedish national guidelines have recommended oral doxycycline for the full treatment duration since 2009 (Albåge et al., 2009). This is mirrored in our study by how 99% of the Swedish physicians use doxycycline for the full treatment course compared to 70% in Norway and 61% in Denmark.

Several randomized studies of NB have found oral doxycycline equally as effective as IV antibiotics in terms of proportion with clinical improvement, decreasing cell count in CSF, and long-term outcome measured at least four months after treatment initiation (Borg et al., 2005; Dotevall and Hagberg, 1999; Karlsson et al., 1994; Kortela et al., 2021; Ljøstad and Mygland, 2010; Ljøstad et al., 2008; Stupica et al., 2021). However, approximately one-fifth of the respondents preferred

IV antibiotics for NB treatment in the current survey. Their choice was based on an assessment of the severity and extent of symptoms, or a desire to rapidly achieve a therapeutic antibiotic concentration in the CNS.

A Norwegian retrospective study from 2017 reported that only 30% of the included NB patients were treated with oral antibiotics for the entire treatment duration (Lorentzen Å et al., 2017). Similarly, a Danish prospective study of 197 patients diagnosed with NB between 2015 and 2017, observed that 39% of patients were administered IV antimicrobials throughout the full treatment course (Nordberg et al., 2020). Our data on preferred antibiotic regimens, indicate that the discrepancy between national recommendations and treatment practice have decreased, especially among the Norwegian respondents but also, although to a lesser extent, among the Danish respondents. The shift towards doxycycline as first choice in treatment of NB patients was also reported by Knudtzen et al. in a retrospective study of 431 Danish patients with NB (Knudtzen et al., 2017). These observations combined may indicate less clinical uncertainty of doxycycline to be as effective as IV antibiotics in this group of patients. Accordingly, we found that among the Norwegian and Danish respondents 5% and 19%, respectively, still preferred a full treatment duration with IV antibiotics. Disadvantages of IV therapy are a higher risk of acquiring venous catheter-related infections, inconvenience for the patient to be admitted and healthcare expenditures.

4.2. Duration of treatment

Most respondents did not treat longer than 21 days (98%) and the preferred treatment duration was 10–14 days (85%). This is in accordance with the EFNS guidelines as well as several national guidelines throughout Europe (Albåge et al., 2009; Helsedirektoratet, 2022; Dansk Selskab for Klinisk Mikrobiologi, 2021; Mygland et al., 2010; NICE, 2018; Rauer et al., 2020). Evidence from various studies does not support deviating from a treatment duration beyond 2–3 weeks for NB (Dersch et al., 2015; Halperin et al., 2007; Oksi et al., 2007). An RCT investigating the outcome in NB patients after two vs. six weeks of treatment with doxycycline is currently under way (Solheim et al., 2019).

In the study by Lorentzen et al. from 2017 only one-third of NB patients in Norway reported a treatment duration of 2 weeks (Lorentzen Å et al., 2017). Most patients received longer treatment. The present study indicates better adherence to treatment guidelines among physicians in Norway, as 66% of the Norwegian respondents reported to prescribe antibiotics for 10–14 days. The reason for extensive treatment may be explained by the Norwegian guidelines recommending 14–21 days in cases of severe affection of the CNS (Helsedirektoratet, 2022). In contrast, 97% of Swedish respondents treated for a duration of 10–14 days, which is in agreement with the Swedish health authorities (Albåge et al., 2009).

The high prioritization score for future RCTs on the use of adjunctive prednisolone therapy in NB patients with facial palsy is in accordance with the lack of data on the subject. Currently, no RCTs on whether additional corticosteroid treatment will improve the overall outcome and time to recovery in NB associated facial palsy has been performed, although NB is a common cause of facial palsy (Engervall et al., 1995; Peltomaa et al., 2002; Rojko et al., 2019). Currently, there is an ongoing Swedish study to evaluate the effect of prednisolone on facial nerve palsy in children diagnosed with NB (Karlsson et al., 2021).

Prednisolone treatment alone or in combination with antiviral therapy has been reported to be beneficial in the treatment of idiopathic peripheral facial nerve palsy (Bell's palsy) and Ramsey Hunt syndrome (reactivation of varicella zoster virus) (Engstrom et al., 2009; Sullivan et al., 2007). A prospective study from Sweden reported no difference in recovery from peripheral facial palsy in a study group of 27 NB patients treated with prednisolone, in addition to doxycycline, compared to a group of historical controls treated only with doxycycline (Avellan and

Bremell, 2021). Similarly, two small studies from Slovenia (Rojko et al., 2019) and the United States (Marques et al., 2022) found no difference in favorable outcome of peripheral facial palsy in NB patients treated with corticosteroids. Two prospective studies conducted in the United States have indicated that corticosteroids worsen the outcome of peripheral facial palsy in NB patients (Jowett et al., 2017; Wormser et al., 2018). However, the sample size in both studies was small and neither study included relevant controls. To demonstrate the potential effect of corticosteroids for peripheral facial palsy in NB patients a larger randomized cohort is needed.

So far RCTs of prolonged antibiotics versus placebo in patients with persistent symptoms despite previous antibiotics treatment for Lyme borreliosis have found no improvement in symptoms (Fallon et al., 2008; Kaplan et al., 2003; Klempner et al., 2001; Krupp et al., 2003). However, clinical uncertainty does still exist, and the responders found more studies to be of importance. This may be explained by the small sample size of the studies with only few NB patients included.

4.3. Limitations

Precautions of the interpretation of the response rate must be kept in mind as it is estimated from the number of e-mails the survey was sent to, which could be both an over- and underestimation.

The survey was sent to approximately 1600 physicians and the estimated total response rate was thus only around 290/1600 (18%). Our study is limited by the potential for selection bias. Physicians who follow national guidelines would be more likely to reply, underestimating the physicians who do not treat in accordance with national guidelines. Furthermore, the present study is limited to physicians taking care of adult patients with NB, although approximately 20% of all patients with NB in Denmark are under the age of 18 years (Hansen and Lebech, 1992).

5. Conclusion

High alignment was found between guidelines in Norway, Sweden, and Denmark. In Sweden, all respondents preferred treating NB with oral doxycycline for 10–14 days, whereas 5% in Norway and 19% in Denmark still treat NB with IV antibiotics for the entire treatment course. RCTs to define the role of adjunctive prednisolone in NB patients with facial palsy and repeated antibiotics in patients with persistent symptoms are prioritized for future research.

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CRedit authorship contribution statement

Emilie Bernardshaw: Formal analysis, Writing – original draft. **Rosa M.M. Gyntheren:** Methodology, Investigation, Writing – original draft, Project administration, Supervision. **Daniel Bremell:** Conceptualization, Writing – review & editing. **Helene Mens:** Conceptualization, Writing – review & editing. **Christian Stenør:** Conceptualization, Writing – review & editing. **Åslaug R. Lorentzen:** Conceptualization, Writing – review & editing. **Jacob Bodilsen:** Conceptualization, Methodology, Writing – review & editing. **Randi Eikeland:** Conceptualization, Writing – review & editing. **Anne-Mette Lebech:** Conceptualization, Methodology, Investigation, Project administration, Funding acquisition, Supervision.

Declaration of Competing Interest

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The other authors declare no conflict of interest.

Data availability

Data will be made available on request.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:[10.1016/j.ttbdis.2022.102051](https://doi.org/10.1016/j.ttbdis.2022.102051).

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