Lyme Hastalığı Tedavisi

Doğrular ve Yanlışlar

Dr. Figen KAPTAN

İzmir Atatürk Eğitim ve Araştırma Hastanesi

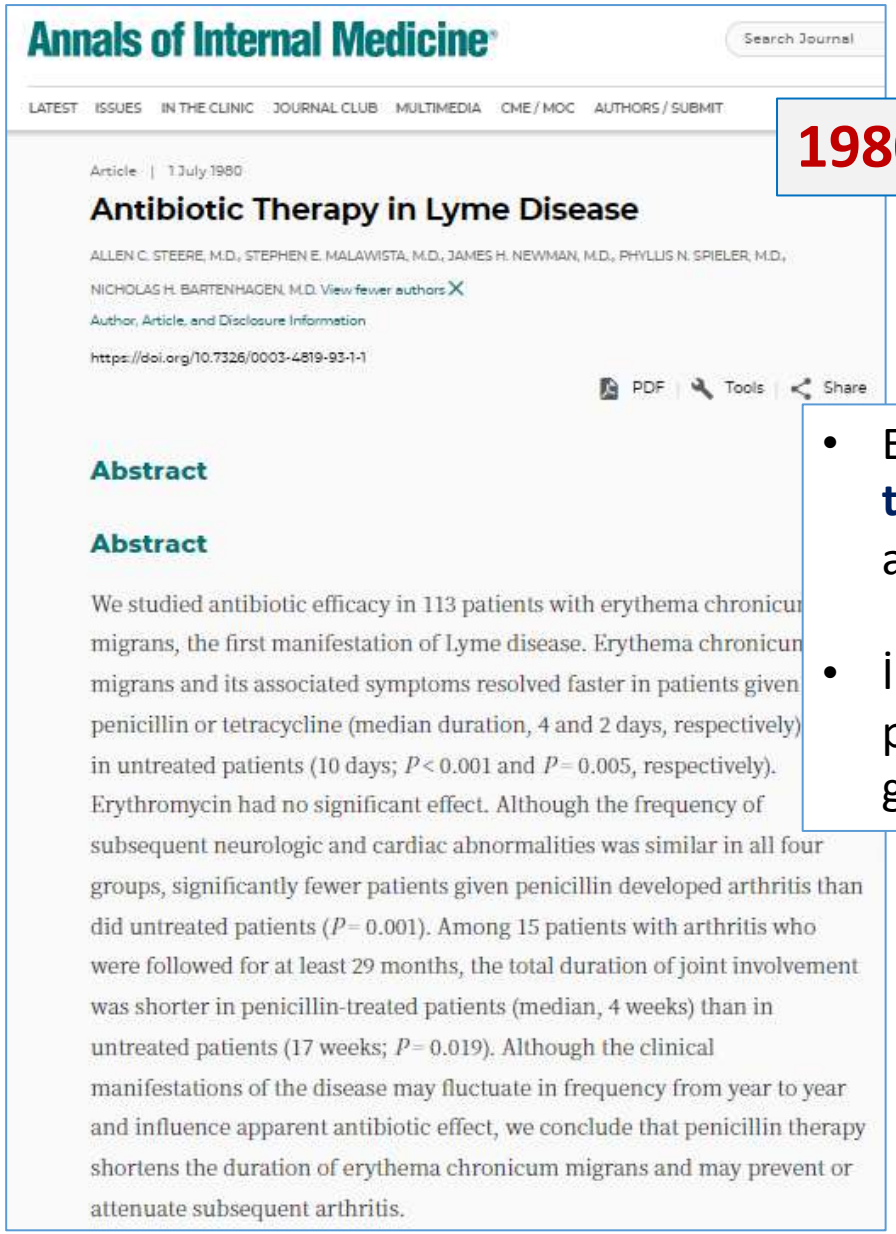
15 Mart 2023, Antalya

1975
Connecticut
RA benzeri semptomlar

1981
William Burgdorfer
Spiroket

1982
Borrelia burgdorferi

Burgdorfer W, Barbour AG, Hayes SF, Benach JL, Grunwaldt E, Davis JP. (1982). Lyme disease-a tick-borne spirochetosis? *Science.* 216(4552), 1317-9.



Annals of Internal Medicine

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1980

Article | 1 July 1980

Antibiotic Therapy in Lyme Disease

ALLEN C. STEERE, M.D., STEPHEN E. MALAWISTA, M.D., JAMES H. NEWMAN, M.D., PHYLLIS N. SPIELER, M.D., NICHOLAS H. BARTENHAGEN, M.D. View fewer authors

Author, Article, and Disclosure Information

https://doi.org/10.7326/0003-4819-93-1-1

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Abstract

Abstract

We studied antibiotic efficacy in 113 patients with erythema chronicu migrans, the first manifestation of Lyme disease. Erythema chronicun migrans and its associated symptoms resolved faster in patients given penicillin or tetracycline (median duration, 4 and 2 days, respectively) in untreated patients (10 days; $P < 0.001$ and $P = 0.005$, respectively). Erythromycin had no significant effect. Although the frequency of subsequent neurologic and cardiac abnormalities was similar in all four groups, significantly fewer patients given penicillin developed arthritis than did untreated patients ($P = 0.001$). Among 15 patients with arthritis who were followed for at least 29 months, the total duration of joint involvement was shorter in penicillin-treated patients (median, 4 weeks) than in untreated patients (17 weeks; $P = 0.019$). Although the clinical manifestations of the disease may fluctuate in frequency from year to year and influence apparent antibiotic effect, we conclude that penicillin therapy shortens the duration of erythema chronicum migrans and may prevent or attenuate subsequent arthritis.

- Eritema migrans: **Penisilin** ve **tetrasiklin** ile semptom süresi anlamlı derecede kısalıyor.
- İleride **artrit gelişme riski** penisilin alanlarda, almayanlara göre, anlamlı olarak **azalıyor**.

LH ile ilişkili bilim dışı ve etik kaygılar

LH savunucuları, bazı tıp uygulayıcıları ve ticari kuruluşların ilişki ve eylemleri, halk sağlığı açısından tehdit oluşturmakta

Lancet Infect Dis. 2011 Sep;11(9):713-9. doi: 10.1016/S1473-3099(11)70034-2.

Antiscience and ethical concerns associated with advocacy of Lyme disease

Paul G Auwaerter [1], Johan S Bakken, Raymond J Dattwyler, J Stephen Dumler, John J Halperin, Edward McSweegan, Robert B Nadelman, Susan O'Connell, Eugene D Shapiro, Sunil K Sood, Allen C Steere, Arthur Weinstein, Gary P Wormser

Affiliations + expand

PMID: 21867956 PMCID: PMC4489928 DOI: 10.1016/S1473-3099(11)70034-2

Free PMC article

Abstract

Advocacy for Lyme disease has become an increasingly important part of an anti
that denies both the viral cause of AIDS and the benefits of vaccines and that su
(sometimes dangerous) alternative medical treatments. Some activists portray Ly
geographically limited tick-borne infection, as a disease that is insidious, ubiquit
diagnose, and almost incurable; they also propose that the disease causes mainl
symptoms that can be treated only with long-term antibiotics and other unortho
treatments. Similar to other antiscience groups, these advocates have created a
alternative selection of practitioners, research, and publications and have coordi
accused opponents of both corruption and conspiracy, and spurred legislative e
evidence-based medicine and peer-reviewed science. The relations and actions
medical practitioners, and commercial bodies involved in Lyme disease advocacy
public health.

Bilim karşıtı hareket

- **Lyme hastalığı savunuculuğu**,
- AIDS'in viral nedenini kabul etmeme,
- Aşıların faydalarını reddetme,
- Kanıtlanmamış (bazen tehlikeli) alternatif tıbbi tedavileri destekleme

Aktivistlerin yaptığı LH tanımı:

- LH: Sinsi, her yerde bulunan, teşhis edilmesi zor, **tedavi edilemez**
- **Uzun süreli antibiyotikle, alışılmışın dışında ve doğrulanmamış tedavilerle tedavi edilebilir**

Aktiviteler:

- Alternatif, sözde bilimsel araştırma ve yayınlar
- Halk protestolarının koordinasyonu
- Muhalifleri yolsuzluk ve komplo kurmakla suçlanma
- Kanıta dayalı tıbbı bozmak için yasama çabalarını teşvik etme

The Clinical Assessment, Treatment, and Prevention of Lyme Disease, Human Granulocytic Anaplasmosis, and Babesiosis: Clinical Practice Guidelines by the Infectious Diseases Society of America

2006

Gary P. Wormser,[1] Raymond J. Dattwyler,[2] Eugene D. Shapiro,[5,6] John J. Halperin,[3,4] Allen C. Steere,[9] Mark S. Klempner,[10] Peter J. Krause,[8] Johan S. Bakken,[11] Franc Strle,[13] Gerold Stanek,[14] Linda Bockenstedt,[7] Durland Fish,[6] J. Stephen Dumler,[12] and Robert B. Nadelman[1]


Richard Blumenthal

Official portrait, 2011

Lyme disease guidelines investigation [edit]

In November 2006, Blumenthal tried, as Paul A. Offit described it, "to legislate a disease, Chronic Lyme, into existence".[73] He launched an antitrust investigation into the Infectious Diseases Society of America's (IDSA's) 2006 guidelines regarding the treatment of Lyme disease.[74] Responding to concerns from chronic Lyme disease advocacy groups, Blumenthal claimed the IDSA guidelines would "severely constrict choices and legitimate diagnosis and treatment options for patients."[75] The medical validity of the IDSA guidelines was not challenged,[76] and a journalist writing in *Nature Medicine* suggested some IDSA members may not have disclosed potential conflicts of interest,[77] while a *Forbes* piece described Blumenthal's investigation as "intimidation" of scientists by an elected official with close ties to Lyme advocacy groups.[78] The *Journal of the American Medical Association* described the decision a... have a chilling effect on future decisions ... review of the guidelines.[80] In 2010, an eight-m... e "medically and scientifically justified" in... me of the language in an executive summary ...

J Med Ethics. 2009 May;35(5):283-8. doi: 10.1136/jme.2008.026526.

Attorney General forces Infectious Diseases Society of America to redo Lyme guidelines due to flawed development process

L Johnson [1], R B Stricker

Affiliations + expand

PMID: 19407031 DOI: 10.1136/jme.2008.026526

Abstract

Lyme disease is one of the most controversial illnesses in the histor... Connecticut Attorney General launched an antitrust investigation i... development process of the Infectious Diseases Society of America... IDSA, the Attorney General noted important commercial conflicts ... scientific evidence that had tainted the guidelines process. This pap... themes that influenced the IDSA investigation. The first is the grow... among guidelines developers, and the second is the increasing centralisation of medical decisions by insurance companies, which use treatment guidelines as a means of controlling the practices of individual doctors and denying treatment for patients. The implications of the first-ever antitrust investigation of medical guidelines and the proposed model to remediate the tainted IDSA guidelines process are also discussed.

Patient groups respond

Members of several Lyme disease patient advocacy groups applauded the outcome of this case.

"The IDSA guidelines are dangerous for patients who suffer long-term Lyme symptoms that do not fall within the IDSA's narrow disease definition," Diane Blanchard, co-president of Time for Lyme, an advocacy group for patients with Lyme disease, said in a press release. – *by Rob Volansky*

Dr. Howard A. Brody
Biyoetik, Aile Hekimi

CORRESPONDENCE

"Chronic" Dishonesty in Medicine?

To the Editor:

With my editorial on dishonesty in medicine only a few months old,[1] new and disturbing evidence of professional misconduct has come to light. On 1 May 2008, the Attorney General of Connecticut, Richard Blumenthal, announced that his antitrust investigation has uncovered serious flaws in the process by which the Infectious Diseases Society of America (IDSA) developed its Lyme disease guidelines.[2] It was the first-ever investigation of a medical society's process of developing guidelines.[3]

Among Blumenthal's findings were the following:

1. The IDSA's guideline panel improperly ignored or minimized medical opinion regarding chronic Lyme disease. As a consequence, serious questions have arisen as to whether the panel's recommendations reflected all of the relevant science available.
2. The IDSA failed to conduct a conflict-of-interest review for any of the participants before their appointment to the 2006 Lyme disease guideline panel. Several of the panelists, however, subsequently disclosed financial interests in drug companies, Lyme disease diagnostic tests, patents, and consulting arrangements with insurance companies.
3. The IDSA allowed the panel chairman, who held a bias against the existence of chronic Lyme disease, to hand-pick a like-minded panel without scrutiny by, or formal approval from, the IDSA's oversight committee.
4. The IDSA also blocked appointment to the panel of scientists and physicians who supported the concept of chronic Lyme disease. According to Blumenthal, a panelist who dissented from the group's position was actually removed in order to achieve "consensus"—a charge denied by the IDSA.[4]

In response to these findings, the IDSA has agreed to create a review panel of 8 to 12 members, none of whom will have served on the 2006 IDSA guideline panel. The IDSA will also conduct an open application process and consider all applicants. Blumenthal and IDSA have agreed to appoint Dr. Howard A. Brody as an ombudsman to ensure that the review panel and its chairperson are free from conflicts of interest. Dr. Brody—a recognized expert and author on medical ethics and conflicts of interest—is director of the Institute for Medical Humanities at the University of Texas Medical Branch in Galveston.

To obtain divergent information, the panel will conduct an open hearing at which all interested parties can make scientific or medical presentations. The hearing will be broadcast live to the public on the Internet via the IDSA's Web site. After col... its review and open hearing, ... whether the data and evidenc... ommendations in the 2006 ... Once the panel has acted on ... will have the option to make ... guidelines in part, or to repla...

The panel's final report will ... SA's Web site. Its content wil... tance, because IDSA guidelines traditionally have a great influence on the medical care of patients who have Lyme disease. Moreover, insurance companies have used these guidelines to justify their restricted coverage of long-term antibiotic treatment of Lyme disease. And, in the past, these guidelines have been widely cited to justify conclusions that chronic Lyme disease does not exist.

Whatever the final report says, Attorney General Blumenthal had this to say:

"Our agreement with IDSA ensures that a new, conflicts-free panel will collect and review all pertinent information, reassess each recommendation and make necessary changes. . . . This Action Plan—incorporating a conflicts screen by an independent neutral expert and a public hearing to receive additional evidence—can serve as a model for all medical organizations and societies that publish medical guidelines. This review should strengthen the public's confidence in such critical standards."

To which I say only, "Amen!"

Herbert L. Fred, MD, MACP,
Professor of Medicine,
The University of Texas Health Science Center at Houston,
Houston, Texas

References

1. Fred HL. Dishonesty in medicine revisited. Tex Heart Inst J 2008;35(1):6-15.
2. Attorney General's investigation reveals flawed Lyme disease guideline process, IDSA agrees to reassess guidelines, install independent arbiter [press release]. State of Connecticut Attorney General's Office; 2008 May 1. Available from: http://www.ct.gov/ag/cwp/view.asp?A=2795&Q=404284
3. Chafez M, Rogers N. Settlement announced in landmark investigation of Lyme disease diagnosis and treatment guidelines [news release]. Lyme Disease Association, Inc.; 2008 May 1. Available from: http://www.lymediseaseassociation.org/NewsReleases/20080501.html
4. Waldman H. Agreement is reached on Lyme disease: short-term treatment will undergo review [news article]. Hartford Courant; 2008 May 2:B1.

Lyme hastalığı tedavisi

İnkübasyon 3-32 gün

PROFİLAKSİ

1. Evre Erken Lokal	**2. Evre** Erken Dissemine	**3. Evre** Geç persistan
Eritema migrans	**Multipl EM** **Sistemik semptomlar** **Nörolojik hastalık** **Kardit** **Borreliyal lenfositoma**	**Lyme artriti (LA)** **Antibiyotik refrakter LA** **Kronik nörolojik bulgular** **ACA**

Persistan semptom

- **Antibiyotik seçimi**
- **Uygulama yolu**
- **Tedavi süresi**

- **Hastalık evresi**
- **Klinik bulgular**
- **Ek tıbbi durumlar, allerji**

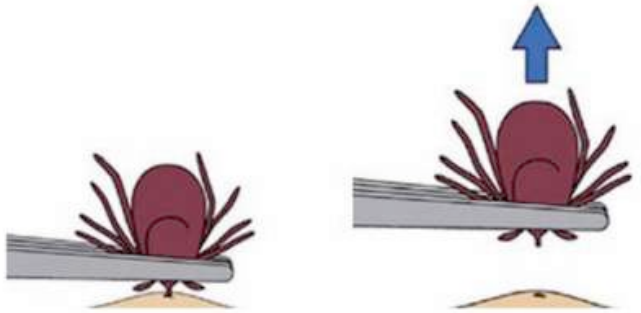
- **Vaktinde tedavi ile başarı ↑**
- **Erken evre: Hızlı ve tam iyileşme**

ACA: Achrodermatitis chronica atroficans.

Yüksek riskli kene ısırığı: Lyme hastalığı kemoprofilaksisi (IDSA 2020)

Yüksek riskli kene ısırığı	Öneriler
• *Ixodes* • Yüksek endemik bölge • Kene ≥36 saat tutunmuş ve büyümüş olmalı	**Doksisiklin:** Tek doz, oral • Kene çıkartıldıktan sonra 72 saat içinde • Erişkin 200 mg • Çocuk 4.4 mk/kg (maksimum 200 mg)

Lantos PM, CID 2021 (IDSA, AAN, ACR: 2020 Guidelines)



ABD: 4 çalışmanın meta-analizi: 1 çalışma 3-19 yaş grubu, **1082 olgu** randomize edilmiş:

- Plasebo ile kıyaslandığında, antibiyotik profilaksisi alanlarda LH riskinde anlamlı azalma:
- **%2.2** (%95 GA %1.2-3.9) vs **%0,2** (%95 GA %0.0-1.0)
- Havuzlanmış odds oranı=0.084; %95 GA, 0.0020-0.57; **p=0.0037**

Tek doz Doksisiklin
10 gün Tetrasiklin
Penisilin
Amoksisilin
vs Plasebo

Warshafsky S, JAC 2010

Avrupa: Tek doz doksisiklin ile profilaksi

ecdc.europa.eu/

Avrupa'da LH'na neden olan *Borrelia* türleri farklı, **Hollanda**, çok merkezli RKÇ

11 Nisan 2013- 10 Haziran 2015; 3538 kene ısırığı (*Ixodes ricinus*) 1648 olgu ITT analiz ile incelenmiş	
Tek doz doksisiklin 200 mg 1041	**Profilaksi almayan** 648
10 olguda LH: **%0.9**	19 olguda LH, **%2.9**

- Rölatif risk **67%** azalmış (%95 GA %31 – 84)
- Tedavi için gerekli sayı: **51** (%95 GA **29 - 180**)
- Ciddi advers olay bildirilmemiş

Harms MG, J Infect 2021

Almanya: Profilaksi

ecdc.europa.eu/

Sebastian Rauer[1]
Stephan Kastenbauer[2]
Heidelore Hofmann[2]
Volker Fingerle[3]
Hans-Iko Huppertz[4,5]
Klaus-Peter Hunfeld[6,7]
Andreas Krause[8]
Bernhard Ruf[9]
Rick Dersch[1,10]
Consensus group

1 German Society of Neurology (DGN), Berlin, Germany
2 German Dermatology Society (DDG), Berlin, Germany
3 German Society for Hygiene and Microbiology (DGHM), Münster, Germany
4 German Society of Paediatrics and Adolescent Medicine (DGKJ), Berlin, Germany
5 German Society of Paediatric Infectology (DGPI), Berlin, Germany
6 The German United Society of Clinical Chemistry and Laboratory Medicine (DGKL), Bonn, Germany
7 INSTAND e.V., Düsseldorf, Germany
8 German Society of Rheumatology (DGRh), Berlin, Germany
9 German Society of Infectious Diseases (DGI), Berlin, Germany
10 Cochrane Germany, Faculty of Medicine, University of Freiburg, Germany

1.3.2 Prophylactic treatment after a tick bite

According to an American study, the risk of infection after a tick bite can be reduced through a one-time prophylactic administration of 200 mg of doxycycline (87% effectiveness) [28], [29]. The results, however, should be interpreted with caution since only one follow-up was conducted after 6 weeks. Thus, no statement can currently be made as to whether this is sufficient with respect to a late infection.

In view of the low risk of disease, a large number of unnecessary doxycycline treatments would have to be accepted in order to prevent one potential infection. According to projections of infection risk in endemic areas, 40–125 prophylaxes would have to be administered in order to prevent 1 disease [30]. Impacts on the intestinal flora and a possible development of resistance through frequent prophylaxis is conceivable. Therefore, oral doxycycline prophylaxis is not recommended in Europe. The prophylactic application of an antibiotic cream is also controversial. Animal studies with azithromycin cream reveal a good prophylactic efficacy [31], [32]. A placebo-controlled study on its effectiveness in humans identified no prophylactic effect [33]. Therefore, this treatment is not recommended.

- AB profilaksisinden sonra izlem süresi kısa
- İnfeksiyon riski düşük
- 1 olası infeksiyonu önlemek için çok sayıda gereksiz tedavi verilecek olması kabul edilmeli
  - Endemik bölgeye projeksiyon:

    1 infeksiyonu önlemek için **40-125 profilaksi**
- Avrupa'da **önerilmiyor**

Floraya etki! Direnç riski!

Azitromisin krem:

Hayvan deneylerinde etkili, insan çalışmalarında etkili değil.

Knauer J, JAC 2011; Piesman J, AAC 2014; Schwameis M, Lancet ID 2017

Guidelines for diagnosis and treatment in neurology – Lyme neuroborreliosis. GMS German Medical Science 2020, Vol. 18, ISSN 1612-3174

Clinical Practice Guidelines by the Infectious Diseases Society of America (IDSA), American Academy of Neurology (AAN), and American College of Rheumatology (ACR): 2020 Guidelines for the Prevention, Diagnosis and Treatment of Lyme Disease

Published CID, 11/30/2020

Clinical Infectious Diseases, Volume 72, Issue 1, 1 January 2021, Pages e1-e48,
https://doi.org/10.1093/cid/ciaa1215
Published (online): 30 November 2020

Paul M Lantos, Jeffrey Rumbaugh, Linda K Bockenstedt, Yngve T Falck-Ytter, Maria E Aguero-

Lyme hastalığı tedavisinde kullanılan antibiyotikler

Per-oral	Günlük Doz	Pediatrik Doz
Doksisiklin	2*100 mg	2*4 mg/kg (azami 100 mg)
Amoksisilin	3*500 mg	50 mg/kg/G (azami 500 mg), üçe bölerek
Sefuroksim aksetil	2*500 mg	30 mg/kg/G (azami 500 mg), ikiye bölerek
Azitromisin	500 mg	10 mg/kg/G (azami 500 mg)
Parenteral	**Günlük Doz**	**Pediatrik Doz**
Seftriakson	2 gr, tek dozda	50-75 mg/kg/G
Sefotaksim	3*2 g/Gün	150-200 mg/kg/G (azami 6 g), 3 veya 4 doza bölerek
Penisilin G	18–24 MÜ/G Her 4 saatte bir olacak şekilde dozlara bölerek	200 000–400 000 Ü/kg/G (azami 18-24 MÜ), Her4 saatte bir olacak şekilde dozlara bölünerek

Önerilen

JH reaksiyonu: Erken dissemine LH'nda, %15 oranında, ilk 24 saat içinde, kendi kendini sınırlar.

Lantos PM, CID 2021 (IDSA, AAN, ACR: 2020 Guidelines)

Lyme hastalığı tedavisi: IDSA, AAN, ACR 2020 Rehberi

	Hastalık Bulgusu	Uygulama	İlaç	Süre, gün (aralık) a
Evre 1	Eritema migrans b	Oral	Doksisiklin	10
			Amoksisilin veya sefuroksim aksetil	14
			Azitromisin c	7 (5–10)
Evre 2	Menenjit, radikülopati	IV d	Seftriakson (Alternatif: Sefotaksim, Pen G)	14–21
		PO	Doksisiklin	14–21
	SS parankim tutulumu	IV	Seftriakson (Alternatif: Sefotaksim, Pen G)	14-28
	Kraniyel sinir felci	Oral	Doksisiklin	14–21
	Kardit	Oral e	Doksisiklin, amoksisilin veya sefuroksim aksetil	14–21
	- Hastaneye yatış	IV e	Seftriakson	14–21
	Borrelial lenfositoma	Oral	Doksisiklin, amoksisilin veya sefuroksim aksetil	14
Evre 3	Artrit			
	- İlk tedavi	Oral	Doksisiklin, amoksisilin veya sefuroksim aksetil	28
	- Rekürran/refrakter artrit	Oral	Doksisiklin, amoksisilin veya sefuroksim aksetil	28
		IV	Seftriakson	14 f
	ACA*	Oral	Doksisiklin, amoksisilin veya sefuroksim aksetil	21–28

*AKA: Achrodermatitis chronica atrophicans

Lantos PM, CID 2021 (IDSA, AAN, ACR: 2020 Guidelines)

Lyme hastalığı tedavisi: Birleşik Krallık, 2018 Rehberi

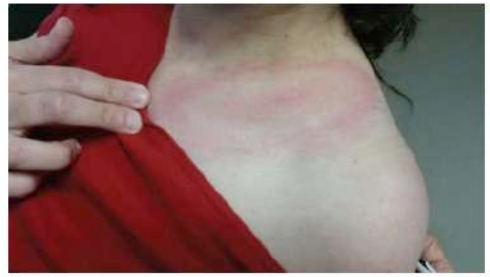
NICE National Institute for Health and Care Excellence

	Erişkin	9-12 Yaş	<9 Yaş
EM (fokal bulgu yok) Non-fokal semptomlar olabilir	1. Doksisiklin 21 gün 2. Amoksisilin 21 gün 3. Azitromisin 17 gün	1. Doksisiklin 21 gün 2. Amoksisilin 21 gün 3. Azitromisin 17 gün	1. Amoksisilin 21 gün 2. Azitromisin 17 gün*
Kraniyel sinir felci, periferik SS tutulumu	1. Doksisiklin 21 gün 2. Amoksisilin 21 gün	1. Doksisiklin 21 gün 2. Amoksisilin 21 gün	Amoksisilin 21 gün
SSS tutulumu	Seftriakson 21 gün **2*2 g/G** veya **1*4 g/G**	1. Seftriakson 21 gün 2. Doksisiklin 21 gün	Seftriakson 21 gün
Artrit	1. Doksisiklin 28 gün 2. Amoksisilin 28 gün 3. Seftriakson 28 gün	1. Seftriakson 21 gün 2. Doksisiklin 21 gün	Seftriakson 21 gün
ACA	1. Doksisiklin 28 gün 2. Amoksisilin 28 gün 3. Seftriakson 28 gün	1. Doksisiklin 21 gün 2. Amoksisilin 21 gün 3. Seftriakson 21 gün	1. Amoksisilin 21 gün 2. Seftriakson 21 gün
Kardit	1. Doksisiklin 21 gün 2. Seftriakson 21 gün	1. Doksisiklin 21 gün 2. Seftriakson 21 gün	Seftriakson 21 gün
Kardit: Hemodinamik olarak stabil olmayan	Seftriakson 21 gün	1. Seftriakson 21 gün 2. Doksisiklin 21 gün	Seftriakson 21 gün

QT uzaması

Lyme disease NICE guideline Published: 11 April 2018 www.nice.org.uk/guidance/ng95

Eritema migrans tedavisi



Tedavisiz kendiliğinden kaybolur AB tedavisi: ▪ Lezyon ve semptomlarda hızlı rezolüsyon ▪ Dissemine hastalık gelişmesi önlenir	ABD, Avrupa Coğrafi bölgeye göre antibiyotik duyarlılığı değişmiyor	Doksisiklin Amoksisilin Sefuroksim aksetil Benzer etkinlik Strle E, Diagn Microbiol Infect Dis 2018

Penisilin V: Avrupa'da amoksisilin ve doksisilin ile benzer etkinlik (Optimal doz: Çalışma gerekiyor)

Azitromisin:

- Birçok çalışmada etkinliği karşılaştırıldığı ilaçlarla benzer
- Amoksisilin ile kıyaslandığı ÇK-RKÇ'da etkinlik daha düşük (%14 olgu: STARI olabilir)*
- ABD'de ikinci seçenek

STARI
southern tick-associated rash illness
Amblyomma americanum

Massarotti EM, Am J Med 1992; Strle F, JAC 1992; Strle F, Infection 1993; Arnež M, Pediatr Infect Dis J 2015; Barsic B,Infection 2000; Strle F, Infection 1996; Weber K, Infection 1993; Arnez M, Wien Klin Wochenschr 2002; Wormser GP, CID 2005; Luft BJ, *Ann Intern Med 1996; *Wormser GP, CID 2005

Eritema migrans tedavisi

Doksisiklin
- Fetal kemik oluşumu üzerine etki
- Dişlerde kalıcı renk değişikliği
- Enamel hipoplazisi

Antibiyotik	Süre
Doksisiklin	10 gün
Amoksisilin	14 gün
Sefuroksim	14 gün
Azitromisin	5-10 gün (ABD: 7 gün)

Doksisiklin

- Amerikan Pediatri Akademisi:
  - Yaşa bağlı olmaksızın doksisiklin, amoksisilin veya sefuroksim aksetil öneriyor.
- Ancak, bazı uzmanlar güvenlik nedeniyle diğer antibiyotiklerin tolere edilemediği durumlarda tercih ediyor.
- Küçük çocuklar (<8 - 9 yaş), gebelik, emzirme:
  - Beta-laktam
  - BL kontrendike ise bireysel olarak karar verilmeli
- Gebelik kategorisi: **D**

Lyme hastalığı: Pediatrik yaklaşım
- **Tek doz**: Dişlerde boyanma olması beklenmiyor. **14 gün**: Rutin önerilmiyor.

Wormser GP, Diagn Microb Infect Dis 2019; Wormser GP, Pediatr Infect Dis 2019

Lantos PM, CID 2021 (IDSA, AAN, ACR: 2020 Guidelines)

Doksisiklin için ısrarcı olalım mı?

AMERICAN SOCIETY FOR MICROBIOLOGY | Microbiology Spectrum

RESEARCH ARTICLE

Forty Years of Evidence on the Efficacy and Safety of Oral and Injectable Antibiotics for Treating Lyme Disease of Adults and Children: A Network Meta-Analysis

Jiaru Yang,[a,b] Shiyuan Wen,[a] Jing Kong,[a] Peng Yue,[a] Wenjing Cao,[a] Xin Xu,[a] Yu Zhang,[a] Jingjing Chen,[a] Meixiao Liu,[a] Yuxin Fan,[a] Lisha Luo,[a] Taigui Chen,[a] Lianbao Li,[a] Bingxue Li,[a] Yan Dong,[a] Suyi Luo,[a] Guozhong Zhou,[a] Aihua Liu,[a,b] Fukai Bao[a,b]

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[b]Yunnan Province Key Laboratory of Children's Major Diseases Research, The Affiliated Children's Hospital, Kunming Medical University, Kunming, China

21 Nisan 2021'e dek

31 RKÇ	2,748 hasta	11 antibiyotik

LH Tedavisi için Etkili	LH Tedavisi için Güvenilir
• Amoksisilin* 1.5 g/G • Azithromisin 0.5 g/G • Seftriakson • Sefotaksim OR aralığı, 1.02 - 1,610.43	• Sefuroksim • Penisilin OR aralığı, 0.027 - 0.98

*EM tedavisi için etkili OR aralığı 1.18 - 25.66

Doksisiklin: Etkinlik ve güvenlik avantajı olduğuna dair kanıt gözlenmemiş;

- LH, artriti, nörolojik hst, EM tedavisi;
- Hem çocuklar, hem erişkinler açısından

AMERICAN SOCIETY FOR MICROBIOLOGY | Microbiology Spectrum

RESEARCH ARTICLE

Forty Years of Evidence on the Efficacy and Safety of Oral and Injectable Antibiotics for Treating Lyme Disease of Adults and Children: A Network Meta-Analysis

Jiaru Yang,[a,b] Shiyuan Wen,[a] Jing Kong,[a] Peng Yue,[a] Wenjing Cao,[a] Xin Xu,[a] Yu Zhang,[a] Jingjing Chen,[a] Meixiao Liu,[a] Yuxin Fan,[a] Lisha Luo,[a] Taigui Chen,[a] Lianbao Li,[a] Bingxue Li,[a] Yan Dong,[a] Suyi Luo,[a] Guozhong Zhou,[a] Aihua Liu,[a,b] Fukai Bao[a,b]

[a]The Institute for Tropical Medicine, Kunming Medical University, Kunming, China
[b]Yunnan Province Key Laboratory of Children's Major Diseases Research, The Affiliated Children's Hospital, Kunming Medical University, Kunming, China

21 Nisan 2021'e dek

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- LH, artriti, nörolojik hst, EM tedavisi;
- Hem çocuklar, hem erişkinler açısından

Review > Diagn Microbiol Infect Dis. 2018 Jun;91(2):156-160.
doi: 10.1016/j.diagmicrobio.2018.01.025. Epub 2018 Feb 2.

Is the risk of early neurologic Lyme borreliosis reduced by preferentially treating patients with erythema migrans with doxycycline?

Franc Strle [1], Daša Stupica [2], Petra Bogovič [3], Paul Visintainer [4], Gary P Wormser [5]

19 çalışma incelenmiş:
EM tedavisi için doksisiklin kullananlarda, erken nörolojik LH gelişme riski:

- **Doksisiklin** karşılaştırıldığı ilaçlara göre daha üstün değil

Nörolojik Lyme hastalığı: Tedavi

Parankim tutulumu yok: 14-21 gün

- ✓ İV: Seftriakson, Sefotaksim, Penisilin G
- ✓ Per-oral: Doksisiklin

Parankim tutulumu var*: 2-4 hf *Fokal bulgular, MRI kanıtı

- ✓ İV: Seftriakson, Sefotaksim, Penisilin G

Penisilin, seftriakson, sefotaksim, doksisiklin:

- Hem erişkin, hem çocuklarda yanıt iyi
- Çoğu çalışma İV ilaçlar ile
- Avrupa: Oral doksisiklin erişkinlerde menenjit, kraniyel nörit ve radikülit için öneriliyor

İV antibiyotik:

- Parankimal SSS tutulumu
- Ciddi nörolojik semptom
- PO tedavi ile başarısızlık

Halperin JJ, Neurology 2007

Lantos PM, CID 2021 (IDSA, AAN, ACR: 2020 Guidelines)

Lyme hastalığı
Menenjit tedavisi için doksisiklin uygun mu?

İsveç, serum ± BOS antikoru pozitif	
İV penisilin, 14 gün	PO doksisiklin, 14 gün
23 hasta	31 hasta

↓

- Tüm hastalar: İyileşme, 1-yıllık izlem skoru, BOS analizi, serolojik ve klinik açıdan fark yok
- Tedavi başarısızlığı yok
- Her iki grupta birer hastada rezidüel semptomlar nedeniyle yeniden tedavi ihtiyacı
- Oral DS **yeterli** ve **maliyet etkin** bir alternatif olabilir

Karlsson M, Neurology 1994

İsveç, 1990-2012, retrospektif, PO doksisiklin Tedaviden önce ve sonra BOS bakılan	
Santral SS infeksiyonu	Periferik SS infeksiyonu
26 hasta	115 hasta

↓

- Tedavi sonrası hastaların tümünde belirgin klinik iyileşme
- İzlem sonunda %62 olguda bazı semptomlar devam etmiş
- **BOS MNL hücre sayısı ↓:** İki hasta grubu arasında anlamlı fark yok

✓

Bremell D, Eur J Neurol 2014

Review > Cochrane Database Syst Rev. 2016 Dec 8;12(12):CD006978.
doi: 10.1002/14651858.CD006978.pub2.

Antibiotics for the neurological complications of Lyme disease

Diego Cadavid [1], Paul G Auwaerter [2], Jeffrey Rumbaugh [3], Harald Gelderblom [4]

Affiliations – collapse

Affiliations

1 Fulcrum Therapeutics, One Kendall Square, Building 700, Suite B7102, Cambridge, MA, USA, 02139.
2 Sherrilyn and Ken Fisher Center for Environmental Infectious Diseases, John Hopkins University School of Medicine, 725 N. Wolfe Street, PTCB - Rm 231, Baltimore, MD, USA, 21287.
3 Watson Clinic, 1600 Lakeland Hills Blvd, Lakeland, FL, USA, 33805.
4 National Association of Statutory Health Insurance Funds, Berlin, Germany.

7 RKÇ, 450 olgu
Avrupa'da yapılan çalışmalar
Amerika: Uygun çalışma yok
Sadece 1 çalışma çift kör
Pediatri: 1 çalışma var

Penisilin G ve seftriakson	4 çalışma
Doksisiklin	3 çalışma
Sefotaksim	2 çalışma
Amoksisilin vs plasebo, 3 ay	1 çalışma

Avrupa'da sık olan suşlar
- *B. afzelii*
- *B. garinii*
- *B. bavariensis*

Kanıt kalitesi düşük/çok düşük
- Sınırlı sayıda çalışma
- Çalışmalar arasında heterojenite yüksek
- Sonlanım ölçekleri farklı

Dissemine Lyme hastalığı
Tedavi süresinin uzatılmasına gerek var mı?

Duration of antibiotic treatment in disseminated Lyme borreliosis: a double-blind, randomized, placebo-controlled, multicenter clinical study

J Oksi [1], J Nikoskelainen, H Hiekkanen, A Lauhio, M Peltomaa, A Pitkäranta, D Nyman, H Granlund, S-A Carlsson, I Seppälä, V Valtonen, M Viljanen

Finlandiya, çift kör, ardışık 152 hasta → İV seftriakson 2 g/G, 3 hafta
145 hasta incelenmiş: Kesin veya olası LH
Kesin tanı olanlar: n=62 nöroborreliyoz; n=45 artrit veya diğer kas/iskelet bulguları, n=4 diğer

Grup	Amoksisilin 2*1 g/G, 100 gün N=73	Plasebo 2*1/Gün, 100 gün N= 72	
Kesin tanı	52/73 (%71.2)	54/72 (%75)	
Mükemmel/iyi sonuç*	49 (%92.5)	47 (%87.0)	
Kötü sonuç*	3 (%5.7)	6 (%11.1)	p = 0.49
Antikor düzeyinde belirgin azalma	%50 olguda	%50 olguda	

*1 yıl sonunda görsel analog ölçek ile değerlendirilmiş.

Dissemine LH: Tedavi süresinin uzatılması, tedavi yanıtını artırmıyor: RR 1.06 (%95 GA .89-1.25)
Advers olaylar ise anlamlı olarak artıyor: RR 3.70 (%95 GA 1.29-10.6)

Eur J Clin Microbiol Infect Dis. 2007

J Neurol Neurosurg Psychiatry. 2022 Jul 27;93(11):1222-1228. doi: 10.1136/jnnp-2022-329724.
Online ahead of print.

Six versus 2 weeks treatment with doxycycline in European Lyme neuroborreliosis: a multicentre, non-inferiority, double-blinded, randomised and placebo-controlled trial

Anne Marit Solheim [1 2], Åslaug Rudjord Lorentzen [3 4], Audun Olav Dahlberg [5 6],

Norveç: Ardışık, başka bir neden bulunamayan LNB olguları
- **Olası** LNB: BOS pleositoz veya intratekal antikor üretimi
- **Kesin** LNB: Her ikisi

Erişkin
Bileşik Klinik Skor (0–64 puan): Başlangıçtan 6 aya kadar

Table 2 Main outcome. clinical improvement 6 months after treatment start as measured by difference in clinical composite sum score from baseline to 6 months

Population		Mean improvement (95% CI) 2 weeks treatment		Mean improvement (95% CI) 6 weeks treatment	P value	Mean difference (95% CI)
Intention to treat	n=52	6.4 (5.5 to 7.2)	n=53	6.4 (5.6 to 7.2)	0.99	0.06 (−1.2 to 1.2)
Per protocol	n=52	6.3 (5.6 to 7.1)	n=51	6.7 (6.0 to 7.4)	0.51	−0.4 (−1.4 to 0.7)

Önceden belirlenen non-inferiority marjı (0.5 puan) gösterilememiş.
Ancak, her iki grupta da sonlanım ölçütlerinin düzeldiği görülmüş
10 ve 12. haftada izlem ölçütleri açısından fark yok:
- Klinik skorlama
- BOS verisi
- Hasta tarafından bildirilen sonuç (anket)

6 hafta tedavi: Y.E biraz daha fazla

2 haftadan daha uzun **doksisiklin** tedavisinin Avrupa nöroborreliyozunda yararı yok

Nörolojik Lyme hastalığı

BOS incelemesi gerekiyor mu?

- Menenjit varlığında önerilen tedavi farklı değil
- Hasta bazında karar verilmeli
- Diğer nedenlerin dışlanması açısından önemli
- Pleositoz varsa tedavi yanıtının izlenmesi
- İntratekal antikor bakılması açısından yararlı
- Kafa içi basıncın değerlendirilmesi
  - Özellikle çocuklarda, psödotümör-benzeri tablo

Fasiyal palsi: Steroid kullanımı

- Rehber öneride bulunmuyor
- Uzlaşma yok
- Kontrollu prospektif çalışma yok

İntrakraniyel basıncın azaltılması

- Papil ödemi: Görme kaybı
- Konvansiyonel yöntemler

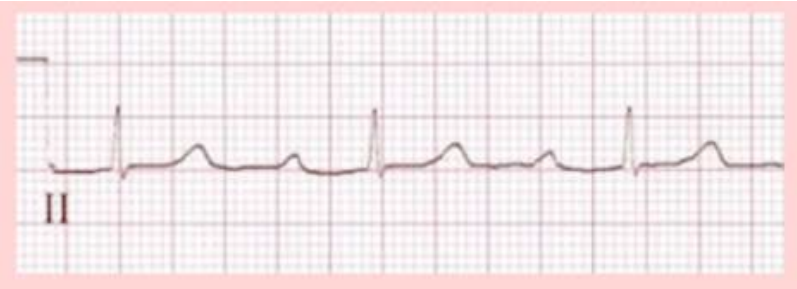
Lantos PM, CID 2021 (IDSA, AAN, ACR: 2020 Guidelines)

Lyme karditi tedavisi

Hastaneye **yatış** endikasyonu:
- Ciddi PR uzaması (>300 msn)
- Aritmi
- Miyoperikardit

→ Kalp bloğu
Taşiaritmi
Miyokardiyal yetmezlik

→ **Ani ölüm**



✓ Sürekli EKG, destek tedavi
✓ Semptomatik bradikardi: Geçici pace
✓ **İV** seftriakson

3-7 gün içinde düzelme olması beklenir
İV tedaviden oral tedaviye geçilebilir

? Adjuvan tedavi: Aspirin, steroid

Kontrollu çalışma yok

Tedavi süresi
14-21 gün

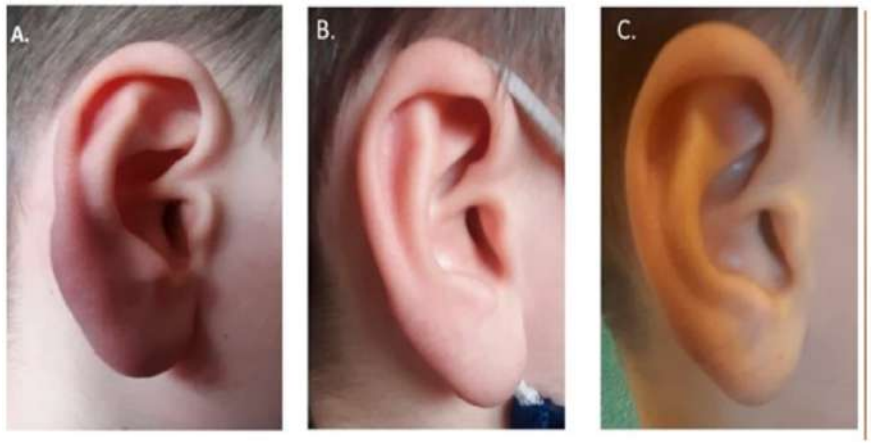
Ayaktan izlem: Oral doksisiklin, amoksisilin veya sefuroksim önerilir.

Lantos PM, CID 2021 (IDSA, AAN, ACR: 2020 Guidelines)

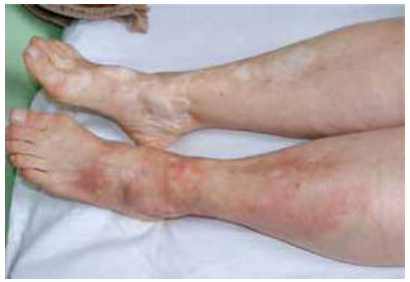
Diğer dermatolojik hastalıklar

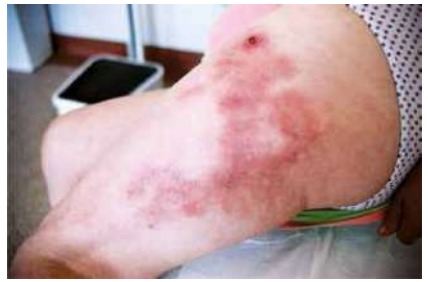
Oral doksisiklin, amoksisilin veya sefuroksim önerilir

Borreliyal lenfositoma: 14-21 gün



Acrodermatitis chronica atrophicans: 28 gün

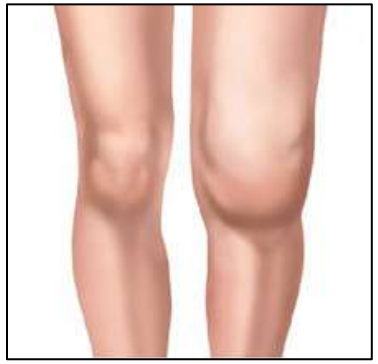




Myszkowska-Torz, A.; Cutaneous Manifestations of Lyme Borreliosis in Children—A Case Series and Review. Life 2023, 13, 72.

Lyme artriti tedavisi

İV seftriakson, sefotaksim İV penisilinden üstün Seftriakson: >28 gün, veri yok	30 gün - per-oral Doksisiklin Amoksisilin Seftriakson 1-3 ay içinde **%90** olguda rezolüsyon (erişkin ve çocuk) Amoksisilin: GİS yan etkisi, allerji	Persistan artrit • HLA-DR4 allotipi • OspA proteinine karşı yüksek IgG oluşumu • Otoantikor oluşumu • TLR1-1805GG polimorfizmi • *B. burgdorferi* RST1 suşu



IDSA 2020: Tedavi süresi 28 gün

- PO: Doksisiklin, amoksisilin, sefuroksim
- İV: Seftriakson

Dattwyler RJ, Lancet 1988; Hassler D, Infection 1990; Steere AC, Arthritis and Rheum 1994

Lyme artriti: Tedavi algoritması

Post infeksiyöz Lyme artriti

- İntra-artiküler glukokortikoid
  - Antibiyotik tedavisi tamamlanmış olmalı
  - Spiroket çoğalmasını arttırabilir — Patchner AR, Ann Neurol1995
  - Bazı çalışmalarda artrit süresi uzamakta — Bentas W, J Rheumatol 2000, Steere AC, Arthritis Rheum 2006
  - AB tedavi başarısızlığı ile ilişkisi: Tartışmalı — Dattwyler RJ, Lancet 1988; Steere AC, Arthritis Rheumatol 1994
  - Pediatri: İkinci basamak tedavide yararlı olabilir
  - "Köprü": DMARD başlamadan önce eklem ağrısı çok fazla ise — Steere AC, J Rheum 2019
- Hastalık modifiye eden antiromatizmal ilaçlar (DMARDs)
- Sinovektomi
  - Diğer tedavilere yanıt yok
  - Tek eklem tutulumu, esas olarak diz
  - Artroskobik sinovektomi ile inflamasyonlu dokunun uzaklaştırılması

Disease Modifying Anti-Rheumatic Drugs (DMARD)

Lyme arthritis in Western Europe: a multicentre retrospective study

Clémence Corre[1] · Guillaume Coiffier[2,3,4] · Benoit Le Goff[5] · Marine Ferreyra[1] · Xavier Guennic[6] · Solène Patrat-Delon[2,7] · Brigitte Degeilh[2,6] · Jean-David Albert[2,3] · Pierre Tattevin[2,6,8,9]

1999-2019

Retrospektif, gözlemsel

52 hasta dahil edilmiş

47 hasta değerlendirilmiş

Yaş: Ort. 43 ± 19.4 yıl

<18 yaş: 9 hasta (%17.3)

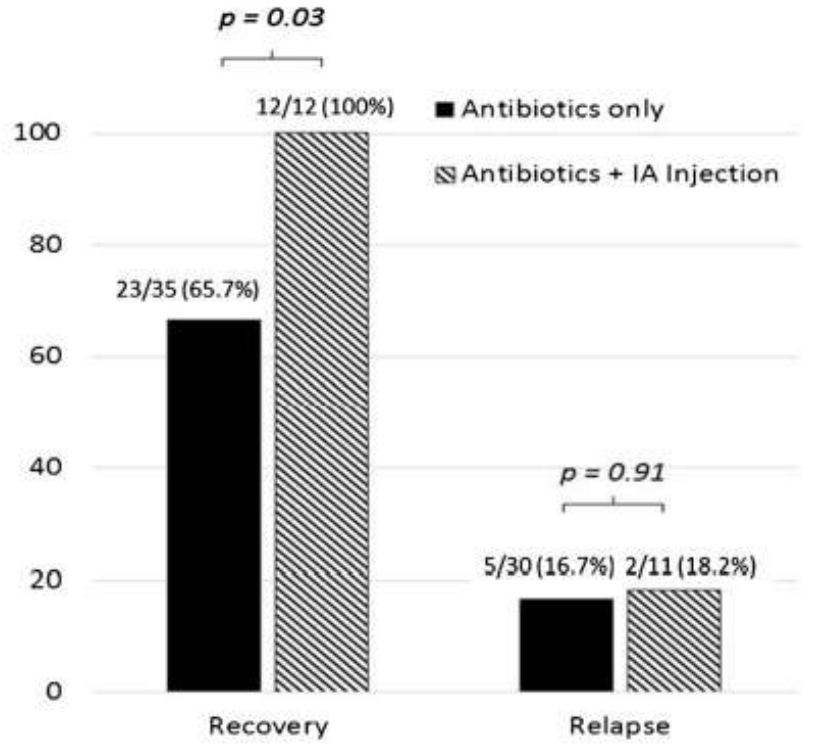


Fig. 3 First-line treatment with antibiotics only versus antibiotics combined with intra-articular injections of corticosteroids: recovery, and relapse rates. IA injection, intra-articular injection of corticosteroids. Note. Numbers are lower for relapses, as the data was not available for 6 patients

İlk basamak tedavi:

AB **+ intra-artiküler steroid**

- ✓ Başarı şansı anlamlı olarak yüksek
- ✓ Steroid injeksiyonu rölaps riskini arttırmıyor

  (vs. sadece AB alanlar)

Eur L Clin Microbiol Infect Dis 2022

İntraartiküler glukokortikoid injeksiyonu:

Pediatrik hastalarda, ikinci basamak tedavide yararlı olabilir.

> J Rheumatol. 2010 May;37(5):1049-55. doi: 10.3899/jrheum.090711. Epub 2010 Apr 1.

Outcomes of children treated for Lyme arthritis: results of a large pediatric cohort

Heather O Tory [1], David Zurakowski, Robert P Sundel

Affiliations + expand

PMID: 20360182 DOI: 10.3899/jrheum.090711

Abstract

Objective: Children often develop arthritis secondary to Lyme disease; however, optimal
Lyme arthritis in pediatric patients remains ill-defined. We sought to characterize the outc
large cohort of children with Lyme arthritis treated using the approach recommended by
American Academy of Pediatrics and the Infectious Diseases Society of America.

Methods: Medical records of patients with Lyme arthritis seen by rheumatologists at a te
children's hospital from 1997 to 2007 were reviewed. Patients were classified with antibiot
responsive or refractory arthritis based on absence or presence of persisting joint involve
months after antibiotic initiation. Treatment regimens and outcomes in patients with refra
arthritis were analyzed.

Results: Of 99 children with Lyme arthritis, 76 had arthritis that responded fully to antibio
developed refractory arthritis. Most patients with refractory arthritis were successfully trea
nonsteroidal antiinflammatory drugs (6 patients), intraarticular steroid injections (4), or di
modifying antirheumatic drugs (DMARD) (2). Five were lost to followup. Six patients with
arthritis were initially treated elsewhere and received additional antibiotic therapy, with n
benefit. Three subsequently required DMARD, while 3 had gradual resolution of arthritis
further therapy. Antibiotic responsiveness could not be predicted from our clinical or labo

Conclusion: Lyme arthritis in children has an excellent prognosis. More than 75% of refer
resolved with antibiotic therapy. Of patients with antibiotic refractory arthritis, none in wh
data were available developed chronic arthritis, joint deformities, or recurrence of infectio
supporting current treatment guidelines.

> Rheumatol Int. 2014 Jul;34(7):987-94. doi: 10.1007/s00296-013-2923-9. Epub 2014 Jan 4.

Intraarticular corticosteroids in refractory childhood Lyme arthritis

S Nimmrich [1], I Becker, G Horneff

Affiliations + expand

PMID: 24390634 DOI: 10.1007/s00296-013-2923-9

Abstract

Lyme arthritis caused by infection with Borrelia burgdorferi is a common late man
borreliosis. Current treatment recommendations include at least one oral or intrav
course, followed by antirheumatic therapy in case of refractory arthritis. We reviev
children with Lyme arthritis who had received antibiotic treatment and assessed o
requirement of antirheumatic therapy. Of a total of 31 patients, 23 (74%) showed
of arthritis after one or two courses of antibiotics, whereas in 8 patients (28%), ste
been performed due to relapsing or remaining symptoms. All of these 8 patients
resolution of symptoms after intraarticular steroid injections. Four of them (50%)
asymptomatic so far with a follow-up period between five up to 40 months. In two
intraarticular corticosteroid injections were required; three patients received addit
treatment with systemic antirheumatic treatment. Patients with antibiotic refractor
higher rate of positivity of the IgG p58 and OspC immunoblot bands ($p = 0.05$) at
Antibodies against OspA, an indicator of later stage infection, occurred more freq
refractory group without reaching significant level. No clinical marker as indicator
prolonged course of Lyme arthritis was identifiable. A quarter of childhood Lyme a
were refractory to antibiotics and required antirheumatic treatment. Intraarticular
childhood Lyme arthritis refractory to antibiotics can lead to marked clinical impro

Intraarticular Glucocorticoid Injection as Second-line Treatment for Lyme Arthritis in Children

Daniel B. Horton, Alysha J. Taxter, Amy L. Davidow, Brandt P. Groh, David D. Sherry, and Carlos D. Rose

ABSTRACT. ***Objective.*** To determine whether second-line intraarticular glucocorticoid (IAGC) injection improves outcomes in children with persistently active Lyme arthritis after initial antibiotics.

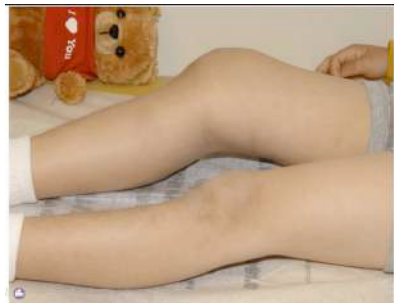
Methods. We conducted an observational comparative effectiveness study through chart review within 3 pediatric rheumatology centers with distinct clinical approaches to second-line treatment of Lyme arthritis. We primarily compared children receiving second-line IAGC to children receiving a second course of antibiotics alone. We evaluated the risk of developing antibiotic-refractory Lyme arthritis (ARLA) using logistic regression and the time to clinical resolution of Lyme arthritis using Cox regression.

Results. Of 112 children with persistently active Lyme arthritis after first-line antibiotics, 18 children received second-line IAGC (13 with concomitant oral antibiotics). Compared to children receiving second-line oral antibiotics alone, children treated with IAGC had similar baseline characteristics but lower rates of ARLA (17% vs 44%; OR 0.3, 95% CI 0.1–0.95; $p = 0.04$) and faster rates of clinical resolution (HR 2.2, 95% CI 1.2–3.9; $p = 0.01$). Children in IAGC and oral antibiotic cohorts did not differ in treatment-associated adverse events. Among children receiving second-line IAGC, outcomes appeared similar irrespective of use of concomitant antibiotics. Outcomes were also similar between intravenous (IV) and oral antibiotic-treated cohorts, but older children seemed to respond more favorably to IV therapy. IV antibiotics were also associated with higher rates of toxicity.

Conclusion. IAGC injection appears to be an effective and safe second-line strategy for persistent Lyme arthritis in children, associated with rapid clinical resolution and reduced need for additional treatment. (First Release June 1 2019; J Rheumatol 2019;46:952–9; doi:10.3899/jrheum.180829)

Horton DB,J Rheumatol. 2019

Pediatrik LA artriti: Cerrahi tedavi "aşırı" uygulanıyor



ORIGINAL ARTICLE

Surgical (over) treatment of pediatric Lyme arthritis: a need for faster *Borrelia* testing

Konopka, Jaclyn A.; Sacks, Hayley A.; Castañeda, Pablo G.; Carter, Cordelia W.

Author Information

Journal of Pediatric

BUY PAP

Abstract

Pediatric Lyme ar
between Lyme an
of this study are t
patients with Lym
single academic i
joint, and positiv
surgically using C
Mean age was 9.5
income >$100 000
operative group v
sedimentation ra
the emergency de
after the surgical
of Lyme arthritis

New York City
2016 – 2021
n=106
Artrit
Çocuk hasta
Yaş ort. 9.5 yıl

n=10 (**%9.4**) septik artrit?

Cerrahi işlem (irrigasyon ve debridman) uygulanan grupta

- Nabız
- Lökosit sayısı, CRP, ESH ve
- Sinovyal hücre sayısı daha yüksek ($p < 0.05$)

- Acile başvuranlarda cerrahi işlem olasılığı daha fazla ($p=0.003$)
- **Lyme testinin sonuçlanması:** Ort. 43.5 saat
  - **Operasyondan 8.7 saat sonra**

911 Akut artrit → **211 LA**: **C6 peptid EİA pozitif/şüpheli:** Duyarlılık %100, Özgüllük %94.2

C6 EİA pozitif veya belirsiz olan 250 hastanın hiçbirinde septik artrit yok: Yanlış tanı/girişim önlenebilir!

Nigrovic LE, Pediatrics 2020

Hastalık modifiye eden antiromatizmal ilaçlar (DMARDs)

- Metotreksat 15-20 mg/hafta
- Hidroksiklorokin 400 mg/gün
- TNFα inhibitörleri: Etanercept, adalimumab

Aktif infeksiyon
Mevcut K.İ. hipoplazisi
Lökopeni
İmmün yetmezlik sendromları

- Etki yavaş, anlamlı yanıt 1-3 ay içerisinde
- Post-antibiyotik LA: 9-14 ay (4 ay – 4 yıl) içinde rezolusyon olmakta
- Uzun süre DMARD kullanılması gerekmiyor
- Genelde 6-12 ay kullanılmakta

Steere AC Arthritis Rheum 2006

Arthritis Rheumatol. 2017 January ; 69(1): 194–202. doi:10.1002/art.39866.

Autoimmune Arthritides, Rheumatoid Arthritis, Psoriatic Arthritis, or Peripheral Spondyloarthropathy, Following Lyme Disease

Sheila L. Arvikar, MD[*], **Jameson T. Crowley, PhD**, **Katherine B. Sulka, BS**, and **Allen C. Steere, MD**
Division of Rheumatology, Allergy, and Immunology, Center for Immunology and Inflammatory Diseases, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts, USA

Abstract

Objective—To describe systemic autoimmune joint diseases following Lyme disease and to compare their clinical features with Lyme arthritis.

Methods—Records of all adult patients referred to our Lyme arthritis clinic over a 13-year period in whom we diagnosed a systemic autoimmune joint disease following Lyme disease were reviewed. For comparison, records of patients enrolled in our Lyme a most recent 2-year period were analyzed. IgG antibodies to *Borrelia* disease-associated autoantigens were measured.

Results—We identified 30 patients who developed a new-onset sys disorder a median of 4 months after Lyme disease, usually erythema rheumatoid arthritis (RA), 13 had psoriatic arthritis (PsA), and 2 had spondyloarthropathy (SpA). The 30 patients typically had polyarthri often had previous psoriasis, axial involvement, or enthesitis. In the patients, monoarticular knee arthritis, without prior EM, was the usu systemic autoimmune patients had positive tests for *B. burgdorferi* Ig they had significantly lower titers and lower frequencies of Lyme-associated autoantibodies than LA patients. Prior to our evaluation, the patients often received additional antibiotics for presumed Lyme arthritis without benefit. We prescribed anti-inflammatory therapies, most commonly disease modifying anti-rheumatic drugs (DMARDs), resulting in improvement.

30 olgu

LH'dan 4 ay sonra

Yeni başlayan sistemik otoimmün eklem hst

↓

15 RA

13 Psöriyatik artrit

2 Periferik spondiloartropati

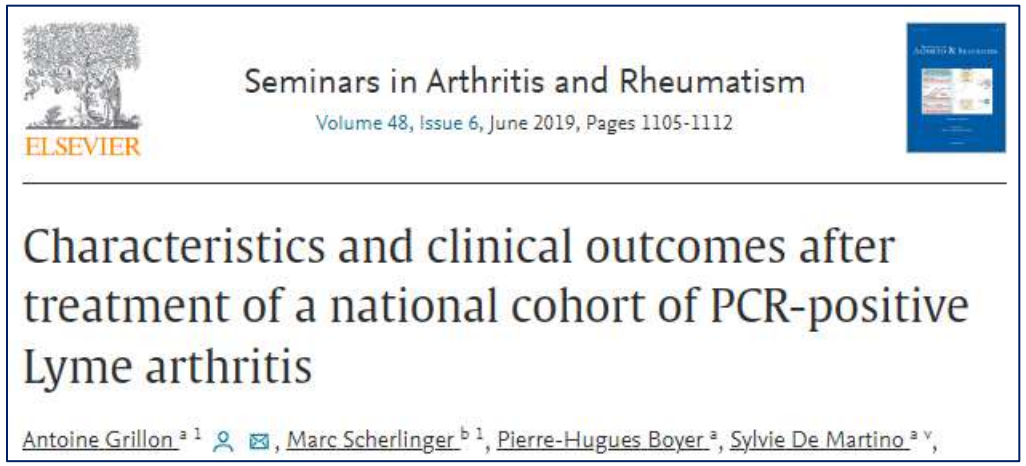
↓

DMARD kullanımı

Tüm olgularda ağrı azalmış

- Persistan infeksiyonun iyileşmiş olduğundan emin olunmalı
- Hasta karara dahil edilmeli

Disease modifying anti-rheumatic drugs (DMARDS)



Seminars in Arthritis and Rheumatism
Volume 48, Issue 6, June 2019, Pages 1105-1112

Characteristics and clinical outcomes after treatment of a national cohort of PCR-positive Lyme arthritis

Antoine Grillon [a 1], Marc Scherlinger [b 1], Pierre-Hugues Boyer [a], Sylvie De Martino [a v],

2010-2016, **Fransa: 357** sinovyal sıvı örneği → **37 örnek** (**%10.4**) *Borrelia* PCR+
35 hasta - DNA bakılmış

%57 *B.b.* sensu stricto
%29 *B. afzelii*
%17 *B. garinii*

Doksisiklin	24
Seftriakson	10
Amoksisilin	6
Sefaklor	1
DS + CTR	5

→ Ortanca 4 (3-12) hf → **n=12** (**%34**) persistan sinovit ortanca 3 (2-16) ay

↓

3 hastada DMARD kullanılmış, remisyon

- *Sistemik inflamatuvar oligo- veya poliartrit*
- *Önceden tutulum olmayan eklemlerde*
- *Persistan infeksiyon bulgusu yok*
- *Kontrol PCR negatif*

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Editorial

Over-treatment in rheumatology

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Introduction

Over-treatment in rheumatology is a serious concern, which can lead to severe toxicity (as sadly exemplified in the USA by the more than 150.000 deadly overdoses of pain-killers [1], fostered by opioid-induced hyperalgesia [2]). Over-treatment can also paradoxically worsen catastrophizing, especially in patients over-diagnosed to justify a drug test. This frequently occurred during the last decade in persons with widespread pain inappropriately diagnosed as spondyloarthritis (SpA) [3], or Lyme disease [4] instead of unclassified polyenthesitis or fibromyalgia. Even when diagnoses of SpA or Lyme are later definitively discarded by their physicians, such patients (as well as their relatives and/or health insurers/employers) can remain convinced that they do suffer from those conditions (since they had been treated for). Last, the undue use of health resources in wrong indications is not desirable for economy, as this money is no longer available for financing treatments with much better cost-utility ratio. Dissecting the mechanisms leading to over-treatment in rheumatology could help and prevent it.

Romatolojide "aşırı" tedavi

Ciddi bir tehlike…

- ABD, ağrı kesicilerin ölümcül yüksek dozda kullanılması (>150.000)
- Opioid ile indüklenen hiperaljezi

Son dekat içinde yaygın ağrı nedeniyle gereğinden fazla "Lyme hastalığı" tanısı…

- Doktorlar tedavi vermeye zorlanıyor
- Hastalar tedavi istemeye teşvik edilmekte
- Kanaat önderleri etki altında
- İlaç şirketi hissedarları hızlı kar sağlamak arzusunda
- Klinik araştırma sonuçları ihtiyatsızca bireysel düzeye aktarılmamalı

Kas-iskelet Ağrısı, Yorgunluk, Kognitif bozukluk

LH?
Başka hst?

- Kronik Lyme Hastalığı
- Tedavi sonrası Lyme hastalığı sendromu
- Uzun süreli semptomlar
- **Standart tedaviden sonra persistan semptomlar**

✓ Tedavi başarısızlığı yoksa
✓ Reinfeksiyon lehine objektif kanıt yoksa
Ek antibiyotik tedavisi önerilmiyor.

Lantos PM, CID 2021 (IDSA, AAN, ACR: 2020 Guidelines)

LB tedavisinden sonra persistan semptom prevalansı

Hollanda: Gözlemsel kohort çalışma, 12 aylık izlem

Güçlü yönleri: - Prospektif, uygun referans kohortları içeriyor,
- Valide edilmiş semptom skorlama ölçekleri kullanılmış

Grup	Persitan semptom prevalansı
N=1084 LH: Doktor tanısı var, tedavi almış EM: %94.8; Dissemine hst: %5.2	**%27. 2,** %95 GA, 24.7- 29.7
N=1942 Son günlerde kene ısırığı var Tedavi almamış	**%23.3%,** **%**95 GA, 21.3-25.3
N=1887 Genel popülasyon	**%21.2**, %95 GA, 19.3-23.1

%3.9 fark
P=0.016

%6.0 fark
p <0.0001

Nisbeten küçük bir hasta alt grubunda, persistan semptomlar ile LB arasında doğrudan veya dolaylı ilişki olabilir.

LB: Lyme borreliyozu

Ursinus et al. / The Lancet Regional Health – Europe 2021

LH'na bağlı persistan semptomların tedavisi için

Avrupa: ÇK-RKÇ

N=280 → 2 hafta seftriakson tedavisi

↓

Doksisiklin 12 hafta	Klaritromisin + HCQ 12 hafta	Plasebo 12 hafta

SF-36 **yaşam kalitesi** ölçeği
Fiziksel bileşen özet puanı

3 çalışma grubu arasında anlamlı fark yok
Uzun süre tedavinin ek yararı yok

Kognitif performans

- Başlangıç, 14, 26 ve 40 hafta sonra
- Nörofizyolojik testler

Uzun süre AB tedavisinin yararı yok

- 12 hafta doksisiklin veya
- 12 hafta klartiromisin + HQC tedavisi alanlarda kognitif performans 2 hafta seftriakson alanlardan daha iyi değil

Berende A, NEJM 2016; Berende A, Neurology 2019

Literatürden örnekler…

- İnternete dayalı olarak kendi kendine LH tanısı koyan **SLE** hastasının ölümü
- Post-Lyme hastalığı sendromu tedavisindeki antibiyotik ve **İV tedavi**lerin neden olduğu advers olaylar
- ABD, kronik LH tanısı ile tedavi edilen hastada **ciddi bakteriyel infeksiyona** bağlı **ölüm**
- Kronik LH tedavisi, seftriaksonun tetiklediği, hayatı tehdit eden **immün hemolitik anemi**
- Kronik LH'da antibiyotik tedavisi: «**DRESS'e hayır de**»
- LH tedavi etmek için pazarlanan **alışılmadık alternatif tedaviler**
- LH'dan şüphelinen, uzun süre antibiyotik alan bir kadın hastada toplum kökenli ***C. difficile*** nedeniyle ölüm
- LH uygun olmayan tedaviye bağlı **ölüm**

Strizova Z, J*oint Bone Spine* 2019; Goodlet KJ, CID 2018; Marzec NS, *MMWR Morb Mortal Wkly Rep*. 2017; De Wilde *Acta Clin Belg*. 2017; Marks CM, J*AMA Intern Med*. 2016; Lantos PM, *CID* 2015; Holzbauer SM, *CID* 2010; Grogg KL, *CID* 2000

Persistans

- **Antibiyotik toleransı:** Logaritmik üreme fazındaki tipik spiroket formdan durağan fazda varyant yuvarlak cisimcik ve mikrokoloni gelişiyor. *E. coli*'den daha persistan

- Durağan fazdaki Bb, hücre duvarı sentezi inh'lerine duyarlı, in-vitro **vankomisin** persistansı önlüyor

- **Daptomisin + doksisiklin + sefoperazon:** In-vitro: Dirençli mikrokolonileri eradike ediyor
  Fare modeli: Persistans eradike ediliyor

Sharma B, AAC 2015; Wu X, AAC 2018; Feng J, PLoS ONE 2015; Feng J, Discov Med 2019

FDA onaylı ilaç kütüphanesi

Persistan *B.burgdorferi*'ye karşı aktivitesi en yüksek ilaçlar

- Amoxicillin[e]
- Doxycycline[e]
- Penicillin G[e]
- Tetracycline[e]
- Ceftriaxone[e]
- Cefuroxime[e]
- Clarithromycin[e]
- Azithromycin[e]
- Daptomycin
- Clofazimine
- Cefoperazone
- Carbomycin
- Vancomycin
- Cephalothin
- Cefotiam
- Cefmetazole
- Cefepime
- Amodiaquin
- Streptomycin
- Ticarcillin
- Cefonicid
- Piperacillin-tazobactam
- Cefdinir
- Ceforanide
- Cefmenoxime
- Bismuth
- Ceftizoxime
- Ceftibuten
- Amphotericin B
- Cefamandole
- Quinine hydrobromide
- Cyclacillin
- Colistin
- Sulfameter
- Tigecycline

Table 1 Activity of top 27 active hits with better activity than the current Lyme disease antibiotics against stationary-phase *B. burgdorferi* persisters [a]

Drugs (50 μM)	Residual viable cells[b]	Residual viable cells[c]	Ratio of green/red fluoresce			
			Primary screening	Rescreening	Rescreening	*P*-value[d]
Control	93%	94%	8.67	8.38	8.59	-
Amoxicillin[e]	76%	76%	7.98	7.86	7.82	1.000000
Doxycycline[e]	75%	67%	7.62	7.35	7.58	0.233596
Penicillin G[e]	75%	68%	7.41	7.68	7.92	0.699416
Tetracycline[e]	54%	50%	7.59	6.14	7.18	0.102366
Ceftriaxone[e]	50%	44%	6.74	6.89	6.78	0.000182
Cefuroxime[e]	49%	43%	6.59	6.84	6.67	0.000317
Clarithromycin[e]	70%	65%	7.70	7.36	7.59	0.038775
Azithromycin[e]	77%	80%	8.33	8.10	7.92	0.071492
Daptomycin	35%	28%	6.10	6.20	6.09	0.000008
Clofazimine	45%	32%	6.56	6.23	6.02	0.000599
Cefoperazone	37%	34%	6.54	6.32	6.23	0.000126
Carbomycin	41%	37%	6.37	6.81	6.32	0.001045
Vancomycin	48%	38%	6.65	6.58	6.37	0.000152
Cephalothin	49%	40%	6.74	6.49	6.55	0.000133
Cefotiam	42%	43%	6.41	7.55	6.21	0.000503
Cefmetazole	-	43%	6.80	7.38	6.00	0.045064
Cefepime	-	44%	6.67	7.16	6.45	0.006368
Amodiaquin	-	45%	6.79	6.44	6.85	0.000946
Streptomycin	-	45%	6.72	6.93	6.76	0.000175
Ticarcillin	-	46%	6.82	6.72	6.93	0.000163
Cefonicid	-	46%	6.86	7.54	6.07	0.067661
Piperacillin-tazobactam	47%	47%	7.18	6.47	6.98	0.009594
Cefdinir	-	48%	6.88	7.51	6.29	0.049107
Ceforanide	-	48%	6.89	7.49	6.33	0.043847
Cefmenoxime	-	48%	6.82	7.59	6.32	0.058674
Bismuth	-	48%	6.94	6.82	6.92	0.000082
Ceftizoxime	-	49%	6.94	6.83	7.03	0.000223
Ceftibuten	51%	49%	6.81	6.78	7.27	0.004888
Amphotericin B	-	50%	7.14	6.88	6.87	0.000783
Cefamandole	-	50%	6.71	7.73	6.52	0.076304
Quinine hydrobromide	-	50%	7.00	6.85	6.88	0.000124
Cyclacillin	51%	53%	6.81	6.88	7.64	0.045210
Colistin	50%	54%	7.15	7.26	7.23	0.000319
Sulfameter		54%	7.13	7.46	6.98	0.009635
Tigecycline	58%	51%	6.98	7.06	6.96	0.001557

[a] Stationary-phase *B. burgdorferi* (7-day old) cells were treated with drugs for 7 days. The line above clarithromycin refers to antibiotics used to treat Lyme disease.
[b] Residual viable *B. burgdorferi* was assayed by epifluorescence microscope counting.
[c] Residual viable *B. burgdorferi* was calculated according to the regression equation and ratio of Green/Red fluorescence obtained by SYBR Green I/PI assay.
[d] *P*-values of the standard *t*-test for the treated group versus a control group treated with amoxicillin, which is known to have poor activity against stationary-phase persisters.
[e] Currently recommended antibiotics for Lyme disease.[5]

Feng J, Emerging Microbes and Infections (2014)

Tamamlayıcı tedaviler

Aktif bileşik
Spesifik aktivite
Toksisite, pK
Çalışmalar gerekli

Doğal ürünler, botanik ilaçlar

Hem durağan, hem çoğalma fazındaki Bb'e etkili

- *Cryptolepis sanguinolenta* (Sarı kök boya),
- *Juglans nigra* (Siyah ceviz),
- *Polygonum cuspidatum* (Japon madımağı),
- *Uncaria tomentosa* (Kedi pençesi),
- *Artemisia annua* (Yavşan otu),
- *Cistus incanus* (Hünnap),
- *Scutellaria baicalensis* (Çin takkesi)

KLİNİK ÇALIŞMALAR GEREKLİ…

Feng J, Leone J, Schweig S, Zhang Y. Evaluation of natural and botanical medicines for activity against growing and non-growing forms of B. burgdorferi. Front Med. (2020)

Esansiyel yağlar

Hem durağan, hem çoğalma fazındaki Bb'e etkili

- Oregano (Mercanköşk, keklik otu, kara kınık),
- Cinnamon Bark (Tarçın kabuğu),
- Clove Bud (Karanfil tomurcuğu),
- Citronella (Limon otu yağı),
- Garlic (Sarımsak),
- Allspice (Yenibahar),
- Myrrh (Mür, reçine sakızı),
- Hydacheim (Çivili zencefil zambak),
- Litsea cubeba (Çin, narenciye kokulu yağ)

Feng J, Shi W, Miklossy J, Tauxe GM, McMeniman CJ, Zhang Y. Identification of essential oils with strong activity against stationary phase Borrelia burgdorferi. Antibiotics. (2018)

LH tedavi etmek için pazarlanan, alışılmadık, alternatif tedaviler

Table 1. Examples of Alternative Medical Therapies Marketed to Patients for the Treatment of Lyme Disease

Categories of Therapy	Examples
Oxygen	Hyperbaric oxygen Hydrogen peroxide Ozone
Energy and radiation	Ultraviolet light Photon therapy "Cold" lasers Saunas and steam rooms "Rife" therapy (electromagnetic frequency treatments) Magnets
Metal/chelation	Mercury chelation and removal Dimercaptosuccinic acid (DMSA) 2,3-Dimercapto-1-propanesulfonic acid (DMPS) Alpha lipoic acid (ALA) Ethylene diamine tetraacetic acid (EDTA) Removal of dental amalgam Colloidal silver Bismuth
Nutritional supplements	Vitamins C and B12 Herbs Garlic, cilantro, Chlorella, Sarsaparilla, Andrographis, Turmeric, Olive leaf, Cat's claw Burnt mugwort (moxibustion) Glutathione Fish oil Magnesium Salt
Biological and pharmacologic	Urotherapy (urine ingestion) Enemas Bee venom Hormonal therapy Dihidroepiandrostenedione, Pregnenolone, Cortisone, Hydrocortisone Synthetic thyroid hormone Lithium orotate Olmesartan Cholestyramine Naltrexone Sodium chlorite (bleach) Intravenous immune globulin (IVIG) Apheresis Stem cell transplantation

Lantos PM, *CID* 2015

LH tedavi etmek için pazarlanan, alışılmadık, alternatif tedaviler

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In-vitro ve murin modeli: Bazı *B. burgdorferi* suşlarının çoğalmasını inhibe ediyor

Lantos PM, *CID* 2015

Sonuç

Ellen Weinstein

- LH, hem akut, hem persistan bulgularla seyreden kompleks bir hastalıktır.
- Hastalık mekanizmaları ile ilgili bilimsel veriler kısıtlıdır, bilinenler kesin olmayıp gelişmeye devam etmektedir.
- Persistan bulgular etkilenen hastaların yaşam kalitesini bozmaktadır.
- Önemli tedavi hedefleri:
  - Hastalık gelişmesinin önlenmesi,
  - Mümkün olduğunca, erken tanı ve erken tedavinin hedeflenmesi,
  - Hastalık progresyonunun önlenmesi ve
  - Diğer durumlarda, hastanın yaşam kalitesinin iyileştirilmesidir.

İlginiz için teşekkür ederim