

If less is good, then more is better?

Doxycycline Treatment Duration and
Post-Lyme Disease Development

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"STIRS THE DEEPEST EMOTIONS AND REVEALS THE MOST UNSETTLING TRUTH."
SAN FRANCISCO CHRONICLE

UNDEROURSKIN

OFFICIAL SELECTION
TRIBECA

OFFICIAL SELECTION
SILVERDOCS

WINNER
BEST DOCUMENTARY
CAMDEN INT'L

WINNER
BEST DOCUMENTARY
DURANGO INT'L

WINNER
BEST DOCUMENTARY
CONOMA INT'L

WINNER
BEST DOCUMENTARY
HOUSTON INT'L

Lyme Disease in BC

- 20 cases of clinical or laboratory confirmed Lyme Disease reported in BC in 2011
- Ten (50%) of cases reported travel and likely acquired their infection outside of BC

IDSA Treatment

- Doxycycline
 - 100 mg twice per day X 10-21 days
- Amoxicillin
 - 500 mg 3 times per day X 14-21 days
- Cefuroxime axetil
 - 500 mg twice per day X 14-21 days

Terminology

- Late Lyme disease
- Chronic Lyme disease
- Post-Lyme disease
 - Patients remain symptomatic after completion of appropriate antibiotic therapy
 - May or may not describe those with well-documented Lyme disease diagnosis
 - Confusion and controversy exist over the frequency/cause/existence of this process

Late and Chronic Lyme Disease

- Late Lyme disease
 - Objective
 - Arthritis or encephalopathy
 - May be untreated or treated patients
- Chronic Lyme disease
 - Subjective
 - Used by some to describe those who have not been diagnosed with Lyme disease
 - Long term antibiotics controversial

Post-Lyme Disease

- IDSA Definition Inclusion Criteria
 - Documented diagnosis
 - Treatment with recommended antibiotic
 - Resolution/stabilization of objective manifestations
 - Symptom onset within 6 months of diagnosis
 - Symptoms persist for at least 6 months after antibiotic completion
 - Symptoms result in reduction of occupational, educational, social, or personal activities

Post-Lyme Disease

- IDSA Definition Exclusion Criteria
 - Active co-infection
 - Objective abnormalities on physical examination, neuropsychologic testing, laboratory, or imagining that may explain the patient's symptoms (a new underlying disease)
 - Fibromyalgia, chronic fatigue syndrome, or unexplained somatic complaints before the onset of Lyme disease

The Controversy



The Controversy

- Beliefs about Lyme disease:
 - Mostly subjective symptoms
 - Usual doses and durations of antibiotics are insufficient
 - Open-ended treatment with multiple antibiotics are needed
 - *Obtained from popular Lyme disease websites, and from public statements and presentations made by some “Lyme literate medical doctors” and activists

Clinical Question

P	Patient with early Lyme disease	
I	Doxycycline < 20 days	
C	Doxycycline > # days than intervention	
O	Efficacy: <ul style="list-style-type: none">• Resolution of early Lyme disease<ul style="list-style-type: none">• Erythema• Symptoms• Post-Lyme disease at >/= 6 months	Safety: <ul style="list-style-type: none">- Dermatological:<ul style="list-style-type: none">- Photosensitivity- Gastrointestinal:<ul style="list-style-type: none">- Anorexia, diarrhea, dysphagia, hepatotoxicity, nausea, pseudomembranous colitis, and vomiting- Hypersensitivity: Rash, urticaria- Discontinuation of therapy due to AE

Search Strategy

Databases	Cochrane, Google, Google Scholar, Embase, Medline, PubMed, IPA
Search Strategy	Lyme disease OR Lyme borreliosis OR Borrelia burgdorferi AND doxycycline
Limits	English, Humans
Results	2 Prospective 2 Retrospective *excluded 1 retrospective trial (did not report doxycycline results independently)

Annals of Internal Medicine

ARTICLE

Duration of Antibiotic Therapy for Early Lyme Disease

A Randomized, Double-Blind, Placebo-Controlled Trial

Gary P. Wormser, MD; Roshan Ramanathan, MD, MPH; John Nowakowski, MD; Donna McKenna, RN, ANP; Diane Holmgren, RN; Paul Visintainer, PhD; Rhea Dornbush, PhD; Brij Singh, MD; and Robert B. Nadelman, MD

Ann Intern Med. 2003;138:697-704.

Wormser et al. 2003

Design	Prospective, SC, R, DB, PC
P	American patients with erythema migrans, 64% male (n=180)
I	Ceftriaxone 2 g IV X1, doxycycline 100 mg po BID X 10 days, and placebo po BID X 10 days (n=60) Placebo injection (5% dextrose) IV X 1, doxycycline 100 mg po BID X 10 days, and placebo po BID X 10 days (n=61)
C	Placebo injection (5% dextrose) IV X 1 and doxycycline 100 mg po BID X 20 days (n=59)
O	<ul style="list-style-type: none">• Primary:<ul style="list-style-type: none">• Post-Lyme Disease at 1 year• Secondary:<ul style="list-style-type: none">• Complete response at 20 days, 3, 12, 30 months• Neurocognitive testing throughout• Adverse effects at 20 days

Wormser GP et al. Duration of antibiotic therapy for early Lyme disease. A randomized, double-blind, placebo-controlled trial. *Ann Intern Med* 2003

**Randomized
n= 180**

**D+C
n=60 (total)**



20 days (n= 52)
2 not available for follow up,
5 non adherent,
1 did not meet inclusion criteria



3 months (n= 48)
5 not available for follow up,
1 intercurrent non-Lyme illness



12 months (n=45)
7 not available for follow up,
1 intercurrent erythema migrans



30 months (n=37)
11 not available for follow up,
4 intercurrent erythema migrans

**D10
n=61 (total)**



20 days (n= 48)
2 not available for follow up,
9 non adherent,
2 took intercurrent antibiotics



3 months (n= 47)
2 not available for follow up,
1 intercurrent erythema migrans



12 months (n=43)
5 not available for follow up,
1 intercurrent erythema migrans



30 months (n=31)
16 not available for follow up,
1 intercurrent erythema migrans

**D20
n=59 (total)**



20 days (n= 45)
14 non adherent



3 months (n= 41)
3 not available for follow up,
1 intercurrent erythema migrans



12 months (n=40)
4 not available for follow up



30 months (n=31)
9 not available for follow up,
4 intercurrent erythema migrans

Note: Red= excluded from PP analysis

Wormser GP et al. Duration of antibiotic therapy for early Lyme disease. A randomized, double-blind, placebo-controlled trial. *Ann Intern Med* 2003

Complete Response

Time	D10 (n=61)	D20 (n=59)	Difference (%) 20-Day Doxycycline vs. 10-Day Doxycycline	95% CI
20 d	34 (70.8)	29 (64.4)	-6.4	(-25.4 to 12.6)
	37 (71.2)	34 (59.6)		
	37 (60.6)	34 (57.6)		
3 m	36 (76.6)	30 (73.2)	-3.4	(-21.6 to 14.8)
	41 (74.5)	39 (75.0)		
	41 (67.2)	39 (66.1)		
12 m	36 (83.7)	30 (75.0)	-8.7	(-26.1 to 8.7)
	44 (86.3)	39 (78.0)		
	44 (72.1)	39 (66.1)		
30 m	28 (90.3)	26 (83.9)	-6.4	(-23.1 to 10.2)
	35 (85.4)	35 (84.5)		
	35 (85.4)	35 (84.5)		

Red= PP, Black = ITT, Blue= ITT (using number randomized)

Wormser GP et al. Duration of antibiotic therapy for early Lyme disease. A randomized, double-blind, placebo-controlled trial. *Ann Intern Med* 2003

Partial Response

Time	D10 (n=61)	D20 (n=59)	
20 d	13 (27.1)	16 (35.6)	"No significant differences in treatment outcome were found among patients at either the 3- or 12-month time points"
	14 (26.9)	23 (40.4)	
	14 (22.9)	23 (39.0)	
3 m	10 (21.3)	11 (26.8)	
	13 (23.6)	13 (25.0)	
	13 (21.3)	13 (22.0)	
12 m	6 (14.0)	10 (25.0)	
	6 (11.8)	11 (22.0)	
	6 (9.8)	11 (18.6)	
30 m	2 (6.5)	5 (16.1)	
	5 (12.2)	6 (14.6)	
	5 (8.2)	6 (10.2)	

Red= PP, Black = ITT, Blue= ITT (using number randomized)

Adverse Effects

	D10 (n=61)	D20 (n=59)
Dermatological:		
Photosensitivity	5	2
Gastrointestinal:		
Anorexia	1	6
Diarrhea	4	5
Dysphagia	0	0
Hepatotoxicity	NR	NR
Pseudomembranous colitis	NR	NR
Nausea	16	12
Vomiting	2	4
Hypersensitivity		
Rash	NR	NR
Urticaria	0	0
Discontinuation of therapy due to AE	1	0

NR= not reported

Conclusions

- Extending doxycycline from 10 to 20 days did not enhance therapeutic efficacy
- 6.5% to 16.1% were partial responders at 30-months
- No evidence for neurologic deficit development in any of the treatment groups

Limitations

- Do not report statistics on their primary outcome (post-Lyme disease at 12m)
- Nonspecific symptoms:
 - A medical explanation other than Lyme disease may exist
- Many patients withdrew
- Neurocognitive results vague

Treatment of Erythema Migrans With Doxycycline for 10 Days Versus 15 Days

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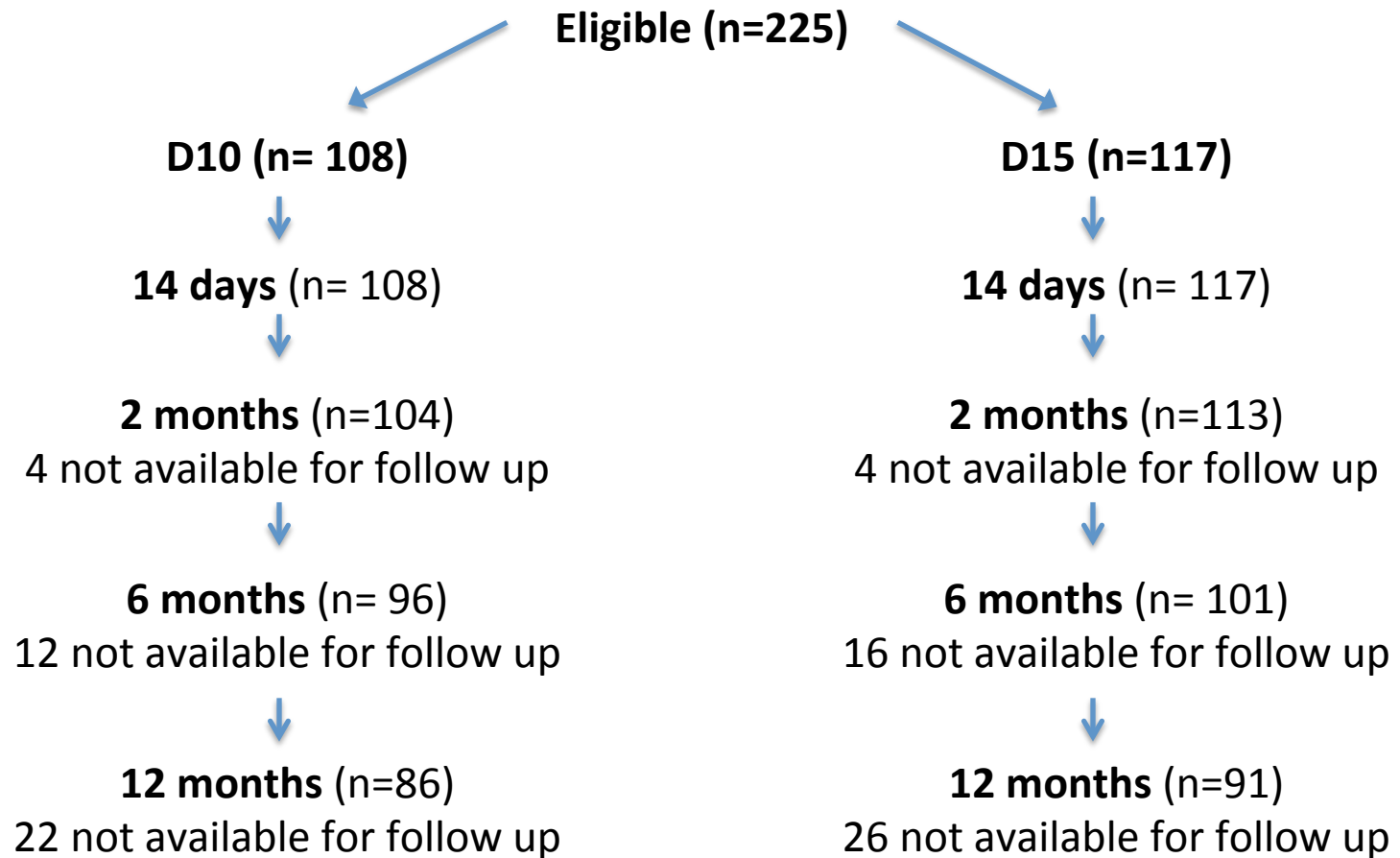
Clinical Infectious Diseases 2012;55(3):343–50

Stupica et al. Treatment of erythema migrans with doxycycline for 10 days versus 15 days. Clin Infect Dis. 2012

Stupica et al. 2012

Design	Prospective noninferiority
P	European patients with solitary erythema migrans, 44% male (n=225)
I	Doxycycline 100 mg po BID X 10 days (n= 108)
C	Doxycycline 100 mg po BID X 15 days (n= 117) Control group (n= 81)
O	Primary endpoints: <ul style="list-style-type: none">• Complete response at 12 months Secondary endpoints: <ul style="list-style-type: none">• Response at 14 days, 2 months, and 6 months• Presence of nonspecific symptoms at 6 months• Adverse events at 14 days• Compliance at 14 days

Stupica et al. 2012

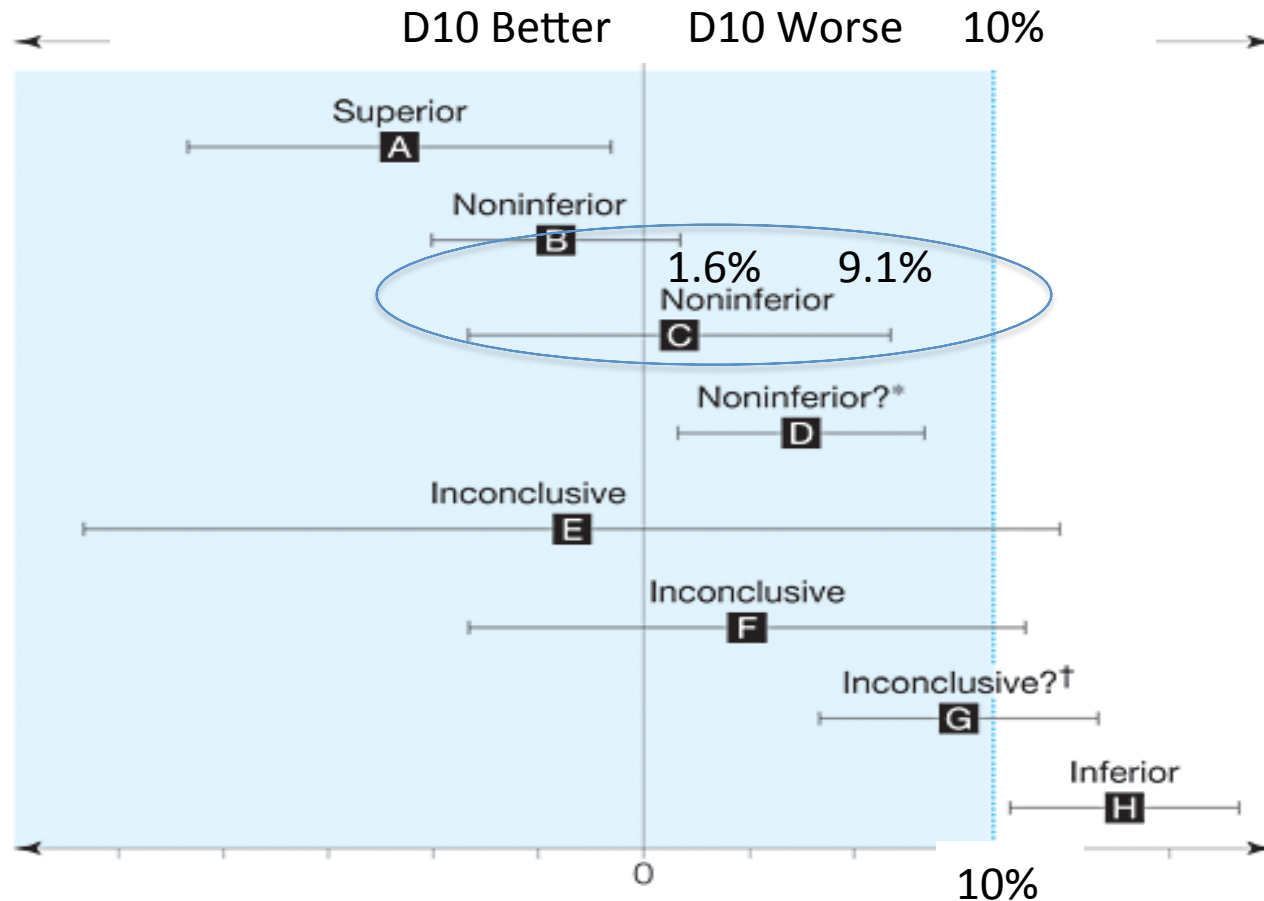


Stupica et al. 2012

Complete Response	D10 (n= 108)	D15 (n=117)	Difference (%)	95% CI upper limit (%)
14 d	60/108 (55.6)	71/117 (60.7)	5.1	16.8
2 m	88/104 (84.6)	98/113 (86.7)	2.1	10.9
6 m	81/96 (84.4)	95/101 (94.1)	9.7	17.9
12 m	79/86 (91.9)	85/91 (93.4)	1.6	9.1

Stupica et al. Treatment of erythema migrans with doxycycline for 10 days versus 15 days. Clin Infect Dis. 2012

Stupica et al. 2012



Difference in Complete Response at 12m
(10 day doxycycline minus 15 day doxycycline)

Stupica et al. Treatment of erythema migrans with doxycycline for 10 days versus 15 days. Clin Infect Dis. 2012

Stupica et al. 2012

Nonspecific symptoms at 6 months	10 days (n= 108)	15 days (n=117)	Controls (n=81)	P
Any	79 (82.3)	72 (71.3)	60 (74.1)	.18
Number of symptoms	6 (1–10.3)	5 (0–9)	6 (0–9)	.51
Symptoms= Fatigue, Malaise , Arthralgias, Headache, Myalgias, Paresthesias, Dizziness, Nausea, Insomnia, Sleepiness, Forgetfulness, Concentration difficulties, Irritability, Pain in spine				

Adverse Effects

	D10 (n= 108)	D15 (n= 117)	P
Dermatological:			
Photosensitivity	0	7 (6%)	0.02
Gastrointestinal:			
Anorexia	NR	NR	NR
Diarrhea	NR	NR	NR
Dysphagia	NR	NR	NR
Hepatotoxicity			
> 10% Increase in bilirubin	28/105 (26.7)	34/109 (31.2)	.55
> 10% Increase in AST	40/105 (38.1)	37/111 (33.3)	.48
Nausea	NR	NR	NR
Pseudomembranous colitis	NR	NR	NR
Vomiting	NR	NR	NR
Hypersensitivity			
Rash	NR	NR	NR
Urticaria	NR	NR	NR
Discontinuation of therapy due to AE	0	0	NR

NR= not reported

Stupica et al. Treatment of erythema migrans with doxycycline for 10 days versus 15 days. Clin Infect Dis. 2012

Conclusions

- 10-day regimen of oral doxycycline was not inferior to the 15-day regimen
- Nonspecific symptoms were similar to control subjects six months after treatment

Limitations

- Generalizability, included patients with solitary erythema migrans
- Nonspecific symptoms:
 - A medical explanation other than Lyme disease may exist
 - Control group at 6 months after enrollment could have Lyme disease
- Power to detect post-Lyme disease?

Doxycycline versus tetracycline therapy for Lyme disease associated with erythema migrans

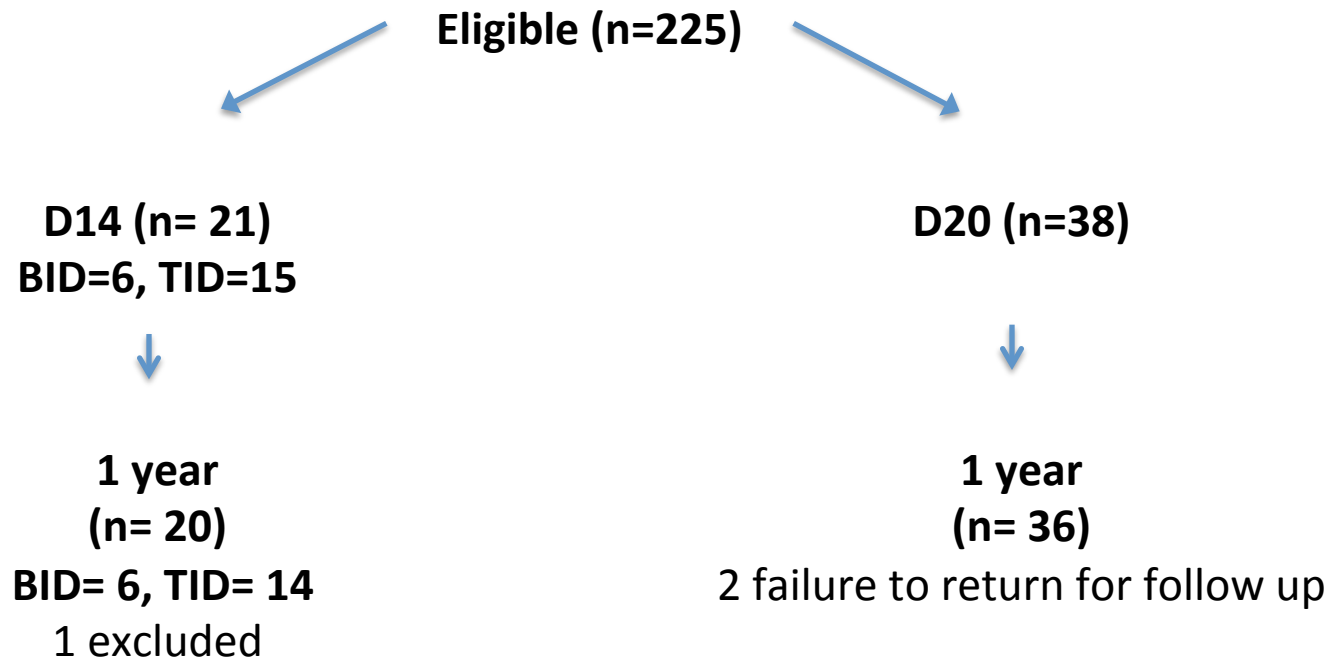
John Nowakowski, MD,^a Robert B. Nadelman, MD,^a Gilda Forseter, RN,^a
Donna McKenna, NP,^b and Gary P. Wormser, MD^a *Valhalla, New York*

Journal of the American Academy of Dermatology
February 1995

Nowakowski J et al. 1995

Design	Retrospective, SC
P	American patients with erythema migrans
I	Tetracycline 500 mg po QID X 14 days (n=27) Doxycycline 100 mg po BID-TID X 14 days (n=21)
C	Doxycycline 100 mg po TID X 20 days (n=38)* * From a prospective study
O	<ul style="list-style-type: none">• Complete resolution of erythema migrans and associated symptoms at 1 month after diagnosis• Whether patients were asymptomatic without repeat treatment 1 year after diagnosis• Safety

Nowakowski J et al. 1995



Nowakowski J et al. 1995

	D14 (n= 20)	D20 (n=36)	Difference (%)	95% CI for diference
Resolution at 30 days	16/20 (80)	23/36 (64)	24	- 1 0 % to 42%
No retreatment and asymptomatic at 1 year	15/20 (75)	26/36 (72)	3	-22% to 28%

Nowakowski J et al. Doxycycline versus tetracycline therapy for Lyme disease associated with erythema migrans. J Am Acad Dermatol. 1995

Adverse Effects

	D14 (n= 21)	D20 (n=38)
Dermatological:		
Photosensitivity	0/21 (0.0)	4/38 (10.5)
Gastrointestinal:		
Anorexia	NR	NR
Diarrhea	1/21 (4.8)	5/38 (13.1)
Dysphagia	NR	NR
Hepatotoxicity	NR	NR
Nausea	6/21 (28.6)	2/38 (7.1)
Pseudomembranous colitis	NR	NR
Vomiting	NR	NR
Hypersensitivity		
Rash	NR	NR
Urticaria	NR	NR
Discontinuation of therapy due to AE	1/21 (4.8)	0/38 (0.0)

NR= not reported

Nowakowski J et al. Doxycycline versus tetracycline therapy for Lyme disease associated with erythema migrans. J Am Acad Dermatol. 1995

Conclusions

- No additional benefit of extending doxycycline from 14 to 20 days
 - Comparable in terms of efficacy and AE
- Propose shorter courses of antibiotics (<14 days) may produce equally satisfactory outcomes

Limitations

- Confounders
 - Looked at age, gender, if patient was symptomatic, and EM duration in baseline demographics
 - Co-morbidities, previous Lyme disease, multiple EM lesions also important
- Recall bias
 - Two different trial designs:
 - D14 patients assessed by telephone interview 12 to 18 months after diagnosis
 - D20 patients assessed in prospective trial and were examined at baseline, during therapy, and at 1,3, and 12 months after diagnosis
- No power calculation, small numbers...

Summary

- Differences:
 - Populations (American vs. European)
 - Inclusion criteria
 - Trial design
 - Definitions of response
 - Frequency and duration of doxycycline
 - Trial duration and follow up

Summary

	D10 vs D20	D10 vs D15	D14 vs D20
Complete response	No difference (20 days, 3, 12, 30 months)	NI (12 months)	No difference (30 days)
Post-Lyme disease	No difference (12 months)	No difference (6 months)	No difference (1 year)
AE	No difference	More photosensitivity	No difference

Summary

- Limitations:
 - ? Adequate power
 - Sample size based on different estimates of response and/or did not meet desired sample size
 - Studies occurred between 1995-2012
 - Variation in standard of care and definitions
 - Results do not apply to:
 - Late-Lyme disease or disseminated disease

Summary

- Trials do not suggest longer initial treatment for early-Lyme Disease:
 - Reduces post-Lyme disease or
 - Increases complete response
- Concern that prolonged treatment may be harmful
 - Photosensitivity higher in one trial
 - Case report of fatality attributed to prolonged therapy

References

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http://www.bcmj.org/sites/default/files/BCMj_53_Vol5_lyme.pdf
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