JOURNAL OF NEUROLOGY AND PSYCHOLOGY RESEARCH

CASE STUDY Open Access

Lyme disease Neurological Implications: IV. Symptoms Management, Treatment, and Human Vaccine Development

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Received date: October 20, 2023, **Accepted date:** October 25, 2023, **Published date:** November 06, 2023.

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Abstract

The evidence-based guidelines for the symptoms management and treatment of Lyme disease patients are reviewed, addressing the usefulness of antibiotic prophylaxis for known tick bites, the effectiveness of erythema migrans treatment, and the role of antibiotic re-treatment in patients with persistent manifestations. It is concluded that whereas it is too early to standardize restrictive protocols, recommendations have been formulated regarding the use, dosage, and regimen of the antibiotic doxycycline. These guidelines apply to the various presentations of the disease (localized, early disseminated, late disseminated, chronic or complex, and post-traumatic syndrome). The issue of lhe long-term benefits of the long-term antibiotic therapy will need to be addressed and resolved. If antibiotics are not the best treatment, a homeopathic treatment has been advocated as a viable alternative. It will be shown that antimicrobial prophylaxis for the prevention of LD may be beneficial in certain circumstances. The history of vaccines and their present status will be assessed. The different research avenues for the development will be explored following different strategies, including transmission-blocking vaccine, targeting the reservoir host, targeting the tick vector and, preferably, blocking Borrelia transmission.

Abbreviations

AB: AntiBodies; Bb: Borrelia Burgdorferi; BBB: Blood-Brain Barrier; Bbl: Borrelial lipoprotein; CLD: Chronic LD: CNS: Central Nervous System; CPG: Clinical Practice Guidelines; CSF: CerebroSpinal Fluid; DbpA= DEAD-box RNA; DRG: Dose–Response Gradient; EM: Erythema Migrans; FDA: (U.S.) Food & Drug Administration; GBS: Guillain-Barré Syndrome;

GRADE: Grading of Recommendations Assessment, Development, and Evaluation; ILADS: International Lyme and Associated Diseases Society; LD: Lyme Disease; LDC: LD Complex; LNB: Lyme Neuroborrelliosis; NIAID: (U.S.) National Institute for Allergy & Infectious Diseases; NIH: (U.S,) National Institutes of Health; OspA, B, C: Outer surface protein A, B, C; OTC: Over-The-Counter; PNS: Peripheral Nervous System; PTLDS: Post-Treatment Lyme Disease Syndrome; RCCT: Randomized Controlled Clinical Trial; RHD: Rheumatic Heart Disease. RMSF: Rocky Mountain Spotted Fever; RS: Reiter's Syndrome; VV: Vaccinia virus.

Keywords

Borrelia Burgdorferi; Lyme disease; Lyme disease complex; Lyme neuroborrelliosis; Lyme vaccine; Post-treatment Lyme disease syndrome.

Introduction

Evidence-based guidelines for the management of Lyme disease (LD) patients were developed to address three clinical questions, namely, the usefulness of antibiotic prophylaxis for known tick bites, the effectiveness of erythema migrans treatment (EM), and the role of antibiotic re-treatment in patients with persistent manifestations of LD. The evidence base for treating LD is best described as sparse, conflicting, a emerging, and assessed as "very low". While it is too early to standardize restrictive protocols, recommendations have been formulated regarding the use, dosage, and regimen of the antibiotic doxycycline. These guidelines undergird the issue of whether and how can LD be treated in any of its stages (localized, early disseminated, late disseminated, chronic LD or LD complex, and post-traumatic LD syndrome). The issue of the long-term benefits of the long-term antibiotic therapy will need to addressed and resolved. If antibiotics are not the best treatment, the (not definitely proven) option could be that of a homeopathic treatment. Antimicrobial prophylaxis for the prevention of LD may be beneficial in certain circumstances. The history of vaccines against LD development dates back over 30 years and their present status will need to be assessed.

Evidence-based guidelines for Lyme symptoms management

Evidence-based guidelines for the management of LD patients were developed by the International Lyme and Associated Diseases Society (ILADS) to replace its earlier 2004 guidelines. They address three clinical questions, namely, the:

- Usefulness of antibiotic prophylaxis: for known tick bites;

- Effectiveness of erythema migrans treatment (EM); and

- Role of antibiotic re-treatment in patients with persistent manifestations of LD.

Although the intended users of the new ILADS guidelines are healthcare providers who evaluate and manage patients with LD, the guidelines could also be of interest to patients themselves for their greater understanding of their condition, the appropriateness of the treatment(s) they are following, and (hopefully) the progress they are making. This would contribute to informing and empowering patients to engage in shared decision-making.

These clinical practice guidelines (CPG) are intended to assist clinicians by presenting evidence-based treatment recommendations, which follow the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system. The GRADE scheme itself is a continually evolving system. The guidelines attempt to incorporate the current state of GRADE. They ensure a transparent and trustworthy guideline process. They are not, however, intended to be the sole source of guidance in managing LD and should neither

be viewed as a substitute for clinical judgment nor used to establish treatment protocols.

But,... what is evidence-based medicine?

Evidence-based medicine is *"the integration of the best available research evidence with clinical expertise and patient values"*. ILADS anticipates performing GRADE assessments on additional topics related to the diagnosis and treatment of tick-borne diseases in the future.

For the reader's information, the GRADE scheme classifies the quality of the evidence as "high", "moderate", "low", or "very low". The quality of evidence is inferred from:

• **Randomized controlled clinical trials (RCCTs):** Initially rated as high, it may be downgraded based on five limitations: (a) study bias, (b) publication bias, (c) indirectness (generalizability), (d) imprecision, and (e) inconsistency; or/and

• **Observational studies:** Generally low, but may be upgraded based on a large effect or dose–response gradient (DRG).

Rather than labeling recommendations as strong or weak, these guidelines use the terms "recommendation" or "strong recommendation" for or against a medical intervention.

What is the evidence quality for LD?

Although LD is not rare, its treatment has not attracted pharmaceutical interest (see sections below on vaccines for LD). The evidence base for treating LD is best described as sparse, conflicting, and emerging. The evidence quality was assessed as "very low". This is consistent with the evidence base for the infectious field as a whole. Indeed, the majority of recommendations in infectious disease medicine generally are based on low-quality evidence.

Evidence-based guidelines for Lyme treatment

The optimal treatment regimen for the management of known tick bites, erythema migrans (EM) rashes, and persistent disease has not yet been determined. Accordingly, it is too early to standardize restrictive protocols. Nonetheless, ILADS does make recommendations for each of these clinical situations:

• **Against the use of a single 200 mg dose of doxycycline for the prevention of LD:** Not only is it unlikely to be highly efficacious, failed therapy in a human trial led to a seronegative disease state;

• **Against the use of 20-day doxycycline treatment for known black-legged tick bites:** (barring any contra-indications). This is based on animal studies;

• **4-6 weeks of antibiotic treatment days for EM rashes:** Antibiotics include doxycycline, amoxicillin or cefuroxime. A minimum of 21 days of azithromycin is also acceptable, especially in Europe. All patients should be reassessed at the end of their initial therapy and, when necessary, antibiotic therapy should be extended.

• **Evaluation for other potential causes before instituting additional antibiotic therapy:** For patients with persistent symptoms and signs of LD.

• **Antibiotic re-treatment:** when a chronic Lyme infection is judged to be a possible cause of the ongoing manifestations and the patient has an impaired quality of life.

Clinical judgment and shared decision-making

Given the number of clinical variables that must be managed and the heterogeneity within the patient

population, clinical judgment is crucial to the provision regarding treatment options must be identified and strongly considered during a shared decision-making process.

Reconciling divergent guidelines

Conflicting guidelines most often result when the pertinent evidence is weak; when developers differ in their underlying values, approach to evidence reviews, synthesis or interpretation; and/or when developers have varying assumptions about intervention benefits and harms. These should be reconciled.

Can LD be treated...and how?

LD treatment varies depending on the stage of the disease as I will now review and discuss.

of patient-centered care. Patient goals and values

Localized (or early) LD

For early LD, a short course of oral antibiotics is curative in the majority of the cases. People treated with appropriate antibiotics in the early stages of LD usually recover rapidly and completely. Antibiotics commonly used for oral treatment include amoxicillin, cefuroxime axetil, or doxycycline, The treatment regimens last 2-3 weeks. In more complicated cases, the disease can usually be successfully treated with three to four weeks of antibiotic therapy. In the case of doxycycline, recent publications suggest greater efficacy for shorter courses of treatment (Table 1).

Treatment regimens listed in the following Table are for localized (or early) LD. These regimens are guidelines only and may need to be adjusted depending on a person's age, weight, medical history, underlying health conditions, pregnancy status, or allergies.

Age category	Drug dosage	Dosage (orally)	Maximum	Duration (days)
Adults	Amoxicillin	500 mg (3 times a day)	N/A	14-21
	Cefuroxime axetil	500 mg (2 times a day)	N/A	14-21
	Doxyxycline	100 mg (2 times a day)	N/A	10-21
Children	Amoxicillin	50 mg/kg per day divided into 3 doses	500 mg/dose	14-21
	Cefuroxime axetil	30 mg/kg per day divided into 2 doses	500 mg/dose	14-21
	Doxyxycline	4 mg/kg per day divided into 2 doses	100 mg/dose	10-21

Adapted from CDC&P

Table 1: Treatment regimens for localized Lyme disease

Note that for people intolerant of amoxicillin, cefuroxime axetil, and doxycycline, the macrolides azithromycin, clarithromycin, or erythromycin may be used, although they have a lower efficacy. People treated with macrolides should be closely monitored to ensure that symptoms resolve. Also, people with certain neurological (or cardiac) forms of illness may require intravenous treatment with antibiotics such as ceftriaxone or penicillin (Table 2).

Medical condition	Alternative treatment
Intolerance of traditional antibiotics (amoxicilin, cefuroxime axetil, or doxyxycline)	Macrolides (azithromycin, clarithromycin, or erythromycin)
Neurological or cardiac forms of illness	Other antibiotics (ceftriaxone, or penicillin)

Table 2: Regimens for people with antibiotic intolerance or neurological illnesses

Early-disseminated LD

Standard treatment typically lasts only four to six weeks, with extensive treatment widely believed to be unwarranted.

Late-disseminated LD

When residual Borrelia reemerges, patients often relapse with LD or more specifically with what is known as chronic Lyme disease (CLD) or, more commonly, Lyme disease complex (LDC). To further complicate matters, most patients diagnosed with LD are unaware or/and ignorant of the full "complex" of co-infections and neurotoxins that reside in their system.

The simultaneous presence of multiple different infections in the body seriously complicates any potential treatment and eliminates the possibility of prescription medication as a viable, singular LD treatment.

Nonetheless, the improvement of the patient's overall symptoms held over time is really the best measure and final indicator of successful CLD treatment.

Post-treatment Lyme disease syndrome (PTLDS)

Although most cases of LD can be cured with a 2-4 - week course of oral antibiotics, patients can sometimes have symptoms of pain, fatigue, joint and muscle aches, or difficulty thinking that last for more than 6 months after they finish treatment. This condition, discussed earlier, is termed “post-treatment Lyme disease syndrome (PTLDS)”. Why some patients experience PTLDS is not known. There are three schools of thought that have tried to explain the situation:

• **Autoimmunity:** Some experts believe that Borrelia burgdorferi can trigger an autoimmune response causing symptoms that last well after the infection itself is gone. This is not an unusual happenstance as autoimmune responses are known to occur following other infections, including campylobacter (Guillain-Barré syndrome, GBS), chlamydia (Reiter’s syndrome, RS), and strep throat (rheumatic heart disease, RHD);

• **Persistent non-LD infection:** Other experts hypothesize that PTLDS results from a persistent but difficult to detect infection; and

• **Other unrelated causes:** Still others believe that the symptoms of PTLDS are due to other causes unrelated to the patient’s *Borrelia burgdorferi* infection.

Patients with PTLDS usually get better over time, but it can take many months to feel completely well. Nonetheless, additional options for managing symptoms may be available.

Again, long-term antibiotic treatment for ongoing symptoms associated with LD can entail possibly serious risks, accompanied by sometimes deadly

complications. After being treated for LD, patients with of active infection. Unfortunately, there is no proven treatment for PTLDS. Studies funded by the (U.S,) National Institutes of Health (NIH) have found that long-term outcomes are no better for patients who received additional prolonged antibiotic treatment than for patients who received a placebo. Worse, long-term antibiotic treatment for PTLDS was found not helpful, has been associated with serious and sometimes deadly complications, and can be dangerous.

The (U.S.) National Institute for Allergy & Infectious Diseases (NIAID) has also looked at the potential benefits of long-term antibiotic therapy, funding three placebo-controlled clinical trials on the efficacy of this prolonged antibiotic therapy. Another trial was conducted in The Netherlands. I summarize below the findings of these four trials.

These trials were designed to ensure that several key parameters were addressed:

• Susceptibility: of Borrelia burgdorferi to the antibiotics used;

• Ability to cross the blood-brain barrier (BBB), access the central nervous system (CNS), and persist at effective levels throughout the course of therapy;

• Ability to kill bacteria living both outside and inside mammalian cells; and

• People receiving antibiotics did report a greater improvement in fatigue than those on placebo. However, there was no benefit to cognitive function.

• Further, six of the study participants had serious adverse events associated with IV antibiotic use, four requiring hospitalization.

Overall, the study authors concluded that additional

PTLDS have non-specific symptoms and no evidence

• Safety and welfare of patients enrolled in the trials.

FIRST CLINICAL TRIAL:

The first clinical trial included two multi-center studies in patients with a well-documented history of previous LD but who reported symptoms common among people reporting PTLDS (persistent pain, fatigue, impaired cognitive function, or unexplained numbness). Patients were treated with 30 days of an intravenous (IV) antibiotic followed by 60 days of an oral antibiotic.

While these studies reinforced the evidence that patients reporting PTLDS symptoms have a severe impairment in overall physical health and quality of life, they provided no evidence of benefit from prolonged antibiotic therapy when compared with placebo.

SECOND CLINICAL TRIAL: (Results published in 2003)

Researchers examined the effect of 28 days of IV antibiotic compared with placebo in 55 patients reporting persistent, severe fatigue at least six months following treatment for laboratory-diagnosed LD.

Patients were assessed for improvements in self-reported fatigue and cognitive function. The study yielded two results:

antibiotic therapy for PTLDS was not supported by the evidence.

THIRD CLINICAL TRIAL:

In this study, the researchers compared clinical improvement following 10 weeks of IV ceftriaxone versus IV placebo. The patients presented with objective memory impairment tests and were treated for LD. In a complicated statistical model, the

ceftriaxone group showed a slightly greater ceftriaxone and the placebo groups had improved similarly from baseline. In addition, adverse effects attributed to IV ceftriaxone occurred in 26% of patients. The authors concluded that because of the limited

FOURTH CLINICAL TRIAL: (conducted in the Netherlands in 2016)

The published results were subjected to rigorous statistical, editorial, and scientific peer review. It was again concluded that in patients with persistent symptoms attributed to LD, longer term treatment with antibiotics did not provide additional benefits compared with shorter term regimens.

The following legitimate questions could be raised following the above results:

Question # 1: If long-term antibiotic therapy is not effective, why do some people report improved symptoms following such treatment? Carefully designed, placebo-controlled studies have failed to demonstrate that prolonged antibiotic therapy is beneficial. Although isolated success stories are possible, such reports alone are not sufficient grounds to support a therapeutic approach. Here, it may well be that a positive response to prolonged antibiotic therapy may be due to the placebo effect, which was reported to be as high as 40% in the studies described above.

Question # 2: Does infection persist after antibiotic therapy? Several recent studies in non-human primates have suggested that Borrelia burgdorferi may persist in animals after antibiotic therapy. Thus:

Study # 1: Remnants of the bacterium remained in mice;

Study # 2: The intact bacterium persisted. (Note: However, it was not possible to culture these bacteria and it is not clear whether they are infectious.);

improvement at 12 weeks, but at 24 weeks both the duration of the cognitive improvement and the risks involved, long-term antibiotic use for PTLDS is not an effective strategy for cognitive improvement. More durable and safer treatment strategies are still needed.

Study # 3: It replicated the earlier finding of persisting DNA but non-cultivatable bacterium using a mouse model; and

Study # 4: Persistent and metabolically active Borrelia burgdorferi was evidenced in rhesus macaques.

In light of these results, it is clear that additional research is needed to learn more about persistent infection in cell culture and animal models, and its potential implication for human disease.

Antibiotics are not the best option for CLD

Conventional Lyme treatment includes weeks or months of antibiotic therapy. This approach not only is proving to be ineffective, it is also potentially harmful with side effects that may include intestinal bleeding, blood clots in the lungs, and anemia. The longer the drugs are taken, the greater the risk of harm. At the least, the antibiotics disrupt the health of the gut bacteria or microbiota, impairing the immune function since at least 70% of the immune system cells reside in the gut. Further, they do not help the joints pain or nerve problems of the infection.

Some people think that the length of time antibiotics are taken makes the difference in their effectiveness. Results are proving otherwise. In two studies of CLD patients, three months of antibiotics were no better than a placebo.

In some cases, the drugs may produce short-term improvement in the ailments but the improvement ceases once the course of antibiotics is finished. So, how does Borrelia burgdorferi escape such intense

treatment? The answer lies in their incredible defenses including the following seven mechanisms:

Mechanism # 1: The Lyme bacteria can change their physical shape, "curling-up" into a ball so antibiotics cannot get into their system and kill them. This cyst form is resilient, and antibiotics are useless against it. Once the threat subsides, the microbes can return to their typical spiral shape.

Mechanism # 2: The Lyme bacteria are able to "talk" to each other. As soon as they detect antibiotics, they send out a distress call to the others. They can wind into cysts before the drugs harm them.

Mechanism # 3: The bacteria can "camouflage" themselves. The immune system notes a microbe's identity by memorizing its protein sequence or genetics. The microbes can alter little parts of their DNA continually changing their appearance, so they do not fit the code. The immune system then has to search for many codes, not one.

Mechanism # 4: The bacteria can "morph" their DNA every time antibiotics are taken. This makes them increasingly resistant to the drugs.

Mechanism # 5: The bacteria shed endotoxins from their cell wall when they die. Antibiotics cannot eliminate these harmful, inflammatory byproducts. Further, antibiotics cannot fix the heightened inflammation.

Mechanism # 6: The bacteria love to hide inside parasites. Just like us, parasites also have a microbiota. While we may have a mix of good and bad microbes in our gut, parasites are a Pandora's box of terrible microbes — one being Lyme. Even if we get rid of Lyme in the rest of our body, the bacteria hiding in parasites can reinfect us. This is why the disease may come back, despite long and intense antibiotic treatment.

Mechanism # 7: To minimize harm from endotoxins and inflammation, the liver and kidneys need support, which antibiotics cannot provide.

Tests for the objective monitoring of treatment response

Unlike blood and intrathecal antibody (AB) tests, cerebrospinal fluid (CSF) pleocytosis tests revert to normal after infection ends. They can, therefore, be used as objective markers of treatment success and inform decisions on whether to treat anew.

Also, in infection involving the peripheral nervous system (PNS), electromyography and nerve conduction studies can be used to monitor objectively the response to treatment.

Separately and independently, genomic testing may greatly help in prescribing the appropriate personalized treatment and accurately track its progress for each patient.

Is there a homeopathic treatment of Lyme and its co-infections?

How to beat CLD?

If antibiotics are not the best CLD treatment, what is? The answer is to work with your body and support the systems that have been overwhelmed. Treatment must address all the contributors to the disease in the right order. By supporting them first, the detoxifying organs will not be overwhelmed when the bacteria start to die. The recommended sequence is:

• Draining pathways;

• Detoxifying organs and the lymphatic system;

• Purge parasites; and

• Combat Lyme bacteria.

which need to work well so they can help in the battle. The colon is the last stop in the body's detoxification system. If bowels are not moved at least 2–3 times a day, every process further up the line will be in jeopardy.

Supporting the colon with intestinal moving herbs is essential as it opens the door for the next step. Once the colon is moving, the liver and kidneys need support. They filter out endotoxins from the dead pathogens. The lymphatic system also needs support, as the bacteria love to live there.

With the described support in place, the parasites that are harboring Borrelia burgdorferi can be tackled. Some researchers have recommended taking parasite-fighting herbs to knock-out this sneaky hiding place of the bacteria. Finally, one is ready to eliminate CLD.

I review below this plant "cocktail" treatment.

The plant "cocktail" treatment

As we know by now, CLD can weaken the immune system, ignite inflammation, squelch energy, provoke pain, and trigger brain fog. It can also generate harmful free radicals, disrupt mitochondria, and overwhelm detoxification pathways. No less than 21 different botanicals have been identified (there may be more), each one offering unique properties and several of them allegedly acting synergistically to help:

- Lower inflammation;
- Reduce joint pain;
- Fight free radical damage;

Lyme is last on the list, not first. Going after it first will only put a heavier burden on the exhausted organs,

- Break up biofilm;
- Decrease viral load;
- Regulate the immune system;
- Purge parasites;
- Support detoxification; and
- Combat Lyme bacteria to beat CLD.

Table 3 provides an overview of these botanicals, indicating their compounds, alleged indication, alleged activity, and other issues. Claimed effects on Lyme and associated co-infections are highlighted. Other alleged benefits for other diseases (such as, for example, malaria) are also indicated for completeness.

(DISCLAIMER: I emphasize that I have not researched these botanicals with regard to their alleged indication, activity, and other uses. Further, I have not ascertained whether they might be considered by the (U.S.) Food & Drug Administration (FDA) as "safe and effective", or as "new drugs" as defined by section 201(p) of the Federal Food, Drug & Cosmetic Act (the "Act") [21 U.S.C. § 321(p)], or be "legally marketed" in conformity with any over-the-counter (OTC) Drug Monograph and related considerations.

All these issues are within the purview and jurisdiction of the FDA. Should any readers intend to use these botanicals, I strongly recommend that they first consult with their physician and the FDA [10903 New Hampshire Avenue, WO51 Silver Spring, Maryland 20993-0002, Website: www.fda.gov; Telephone: 1 (888) 463-6332]).

Plant name	Compound	Indication	Activity	Other uses
1. *Artemisia annua* (sweet wormwood)	Artemisinin	o Anti-parasitic o Anti-oxidant	o **Lyme bacteria** (including cyst forms) o ***Babesia*** (Lyme co-infection). Also: o *Schistosoma* o *Plasmodium* (malaria) o *Toxoplasma gondiio*	After 1 week, left alive ~24% Borrelia cysts. By contrast: ciprofloxacin and doxycycline left 28$-49%
2. Astragalus membranaceous **root**	Phytochemicals (flavonoids, saponins)	o Immune stimulant o Anti-inflammatory o Anti-oxidant	o Breaks up **biofilm**	o Candida o Several pathogenic bacteria
3. Black walnut green huls *(Juglans nigra)*	Phytochemicals (Juglone)	o Anti-microbial o Anti-oxidant o Anti-parasitic o Anti-fungal	Kills ***Borrelia*** **bacteria** (spirochete, cyst, and biofilm)	Yeast *candida albicans*
4. Buckthorn bark *(Frangula alnus)*	Phytochemicals (polyphenols, flavonoids, saponins)	o Anti-oxidant o Anti-viral o Anti-bacterial o Anti-fungal	Disrupts **biofilm**	Laxative
5. Boneset (*Eupatorium perfoliatum* or fever wort or sweating plant)	Phytochemicals	o Anti-inflammatory o Anti-oxidant o Anti-bacterial o Anti-viral	Supports against seasonal viruses to help immune system in **CLD**	o Anti-cancer o Anti-malaria o Fever and cold (in Europe) o Sweat inducer
6. Cat's claw bark *(Uncaria tementosa)* Native to tropical rain forests	Phytochemicals	o Immune system helper o Anti-oxidant o Anti-viral o Anti-inflammatory	Regulates **immune function**	o Peru's “life-giving” plant o Rheumatoid arthritis (significant reduction in joints pain)
7. Cranesbill root *(Geranium maculatum)*	Phytochemicals (tannins)	o Anti-bacterial o Anti-viral o Anti-protozean parasites o Anti-oxidant	Fights ***Borrelia*** **parasites**	Geranium species for: o Cough o Diarrhea o Fever o Parasitic roundworms o Rashes
8. Devil's claw *(Harpagophytum procumbens)*	Phytochemicals	Anti-inflammatory	**Lyme's joints inflammation and pain** (especially knees): ~ 90% of cases	<u>In Africa</u>: o Allergies o Indigestion, and o Liver and kidney issues o Pain <u>In other countries</u>: o Arthritis: ~ 37% drop in knee pain
9. Essiac blend	Burdock root + Indian rhubarb root + sheep sorrel leaves + slippery elm bark	o Anti-oxidant o Prevents free radical damage to cellular DNA	Regulates/normalizes **immune responses**	o Combination of 4 herbs created by the Ojibwa tribe in Canada o Popular alternative cancer therapy

				o Quenches highly reactive hydroxyl-free radicals
10. Eleuthero (root) (Siberian ginseng *senticosus, Acanthopanax senticosus)*	Phytochemicals	o Anti-inflammatory o Pain reducer	o **Lyme pain and inflammation** o Moves stagnant ***Borrelia*** **toxins** through lymphatic system o **Balancing effect on immune system**	o Not a true ginseng o A staple in traditional Chinese medicine o Calms the mind o Increases energy o Strengthens spleen o Supports kidneys
11. Hawthorn berry leaf *(Crataegus monogyna* or *C. laevigata)*	Phytochemicals	o Anti-oxidant	o **Lyme carditis** (~ 10% of cases)	o Cardiovascular problems (heart failure, high blood pressure, irregular heart beat) o Reduces heart palpitations, difficulty breathing o Supports blood flow
12. Horsetail plant *(Equisetum arvense)*	Phytochemicals	o Anti-inflammatory (including reducing arthritic inflammation) o Anti-microbial	**Lyme inflammation**	o One of the oldest plant species on Earth o Strong effect on several bacteria/fungi (including *Candida albicans*)
13. Japanese knotweed root *(Fallopia Japonica* or *Polygonum cuspidatum)*	Phytochemicals (resveratrol)	o Anti-inflammatory (increased regulation of T-cells) o Anti-cancer o Anti-oxidant	Kills ***Borrelia spirochetes***	o Considered troublesome weeds in Europe, North America, and Australia o Can boost regulatory T-cells by 47%
14. Milk thistle seed *(Silybum marianum)*	Silymarin	o Anti-inflammatory o Anti-oxidant o Anti-viral	o **Liver protection in Lyme disease** o ***Babesia***	Protects liver (more than 2000 years)
15. Nettle leaf *(Urtica dioica)*	Phytochemicals (polyphenols)	o Anti-bacterial (including *Candida albicans*) o Anti-inflammatory	o **Lyme joints pain and arthritis** o Supports **immune system**	o Known worldwide o Allergies (seasonal) o Bladder infections o Prostate enlargement o Skin rashes
16. Pau d'Arco barc (Tahebo from the *Tabebuia impetiginosa tree)*	Phytochemicals (beta-lapachione)	o Anti-inflammatory o Anti-parasitic	**Lyme inflammation**	o Native of South America's tropical rain forests o Arthritis o Fever o Fights parasites (*Leishmania*, helminths) o Pain
17. Teasel root *(Dipsacus asperoides)*	Phytochemicals	Anti-inflammatory	o **Lyme joints inflammation** o Directly effective against **Borrelia**	o Pain: back, knee, liver, bruises o Inhibits macrophages from

			spirochetes (~ 95% inhibition within 4 days)	releasing inflammatory compounds
18. Wormwood *(Artemisia absynthium)*	Phytochemicals	o Anti-inflammatory o Anti-parasitic	**Parasites carrying *Borrelia***	o Related to herb #1 o Like sage o As effective as the drug Praziquantel against the common intestinal tapeworm (*Hymenolepsi nana)* o Crohn's disease (80% remission within 6 weeks) o Digestive disorders o Gut inflammation
19. While willow bark *(Salix alba)*	Phytochemicals (Salicilin, similar to aspirin)	o Anti-fever o Anti-inflammatory	**CLD pain and inflammation**	o Known since ancient times o Back pain relief (39% complete relief)
20. Yellow dock root *(Rumex crispus)*	Phytochemicals (Napodin)	**Biofilm inhibitor/buster**	**Lyme detoxification** (*Borrelia* bacteria)	o Inhibits *Candida albicans* o Laxative o Liver function o Malaria combatant (*Plasmodium falciparum)*
21. Turmeric *(Curcumalonga)*	Phytochemicals (curcumin)	o Anti-inflammatory o Anti-oxidant o Anti-parasitic	**Lyme's joints pain and arthritis**	o Combats arthritis o 49% drop in *Schistosoma mansoni* worms

Source: Data from Drs. Todd Watts and Jay Davidson

Table 3: Botanicals for Lyme treatment and claimed characteristics

As supplements, the above plants have unfortunately not been submitted to the rigorous testing required of pharmaceutical drugs. While many of the benefits claimed for them have been demonstrated in isolated studies, the equivalents of clinical trials are sorely needed, especially in the case of Lyme patients.

Antimicrobial prophylaxis for the prevention of LD

Antimicrobial prophylaxis for the prevention of LD following a tick bite can be started within 72 hours of tick removal. It may be beneficial in certain circumstances. A single dose of the antibiotic doxycycline can lower the risk of LD when:

- The tick bite occurred in a State where LD incidence is high (Maryland, Massachusetts, Minnesota, Missouri, New York, Pennsylvania, Virginia, West Virginia, and Wisconsin) or in an area where >20% of ticks are infected with Borrelia burgdorferi, and the patient has no contraindication to doxycycline. The local health department can usually provide information about tick infection rates in its area;

- If a person is suspected of acute tick-borne disease, including early LD or Rocky Mountain spotted fever (RMSF), treatment should be initiated as soon as possible, rather than waiting for laboratory results, which may be insensitive in early illness;

- Location of tick exposure can guide the differential diagnosis;

- The attached tick can be identified as an adult or nymphal black-legged tick;

- The estimated time of attachment is ≥ 36 hours based on the degree of tick engorgement with blood or likely time-of-exposure to the tick; and

- The patient has no contraindication to doxycycline.

Prophylaxis can be started within 72 hours of tick removal (see Table 4). It is to be noted that antibiotic treatment following a tick bite is not recommended as a means to prevent tick-borne diseases other than LD (such as anaplasmosis, babesiosis, ehrlichiosis, and RMSF). There is no evidence this practice is effective, and it may simply delay the onset of disease.

Age category	Drug	Dosage	Maximum	duration
Adults	Doxycycline	200 mg orally	N/A	Once
Children (weighting less than 45kg)	Doxycycline	4.4 mg/kg orally	200 mg	Once (Note: ILADS is against this use)

Source: ILADS: International Lyme and Associated Diseases Society

Table 4: Recommended Lyme disease post-exposure prophylaxis

LD vaccine development

Vaccination against infection is a highly effective means to control the spread of disease in a population. In general, vaccines in common use protect against highly transmissible diseases. Their effectiveness is largely based on the generation of "herd" immunity. In the case of LD, we are dealing with a disease that is not readily transmitted from person-to-person, is vector-borne, and its risk is largely influenced by geography. Nonetheless, despite these limitations to contagion, LD has become a serious and expensive public health problem.

Before dwelling on this highly specialized subject, it would be of interest to provide a brief background.

Background

The impetus for development of a vaccine against LD gained momentum in the 1990's. Two large pharmaceutical companies had devoted considerable effort to it, leading to the approval of the first LD vaccine for human use. Double-blind, randomized, placebo-controlled clinical trials—the most rigorous type of clinical trials - were completed for each of two Borrelia burgdorferi vaccines manufactured by Glaxo-Smith-Kline (GSK), formerly Smith-Kline-Beecham (SKB) and Pasteur-Merieux-Connaught (PMC). Each

study involved more than 10,000 volunteers from areas of the U.S. where LD is common. Both vaccines were so-called recombinant vaccines against LD that were based on a specific part of Borrelia burgdorferi called outer surface protein A (OspA). The vaccines were found to be 49%-68% effective in preventing LD after two injections and 76%-92% after three injections. They were also found to be 100% effective on children. The side effects were only mild or moderate as transient adverse events. The duration of the protective immunity generated in response to the vaccines is not known. The SKB vaccine was ultimately licensed as LYMErix and approved by the FDA on 21 December 1998.

The vaccine was marketed in the U.S. between 1998 and 2002. Its entry in clinical practice was slow for a variety of reasons, including its cost, which was often not reimbursed by insurance companies. Subsequently, hundreds of vaccine recipients reported they had developed autoimmune and other side effects, which some believed were attributed to specific segments of the vaccine protein. Supported by some advocacy groups, a number of class-action lawsuits were filed against GSK, alleging the vaccine had caused these health problems.

These claims were investigated by the FDA and the CDC&P, which found no connection between the vaccine and the autoimmune complaints. Further, the adverse event rate was not found to be elevated among vaccine recipients.

Despite the lack of evidence that the complaints were caused by the vaccine, sales plummeted and LYMErix was withdrawn from the U.S. market by GKS in February/April 2002. On the market for only 4 years, it was pulled in the setting of negative media coverage and fears of vaccine side effects. Several factors led to its failure. GSK then announced that even with the incidence of LD continuing to rise, sales for LYMErix declined from about 1.5 million doses in 1999 to a projected 10,000 doses in 2002. It, therefore, discontinued manufacturing the vaccine, citing insufficient consumer demand.

The fate of LYMErix was described in the medical literature as a "cautionary tale". An editorial in the fame Nature journal cited the withdrawal of LYMErix as an instance in which "unfounded public fears placed pressures on vaccine developers that go beyond reasonable safety considerations." The original developer of the OspA vaccine at the Max Planck Institute in Germany told Nature: "This just shows how irrational the world can be... There was no scientific justification for the first OspA vaccine LYMErix being pulled". This prompted the renowned vaccinologist Stanley Plotkin to publish an article in 2011 in which he called the removal of the Lyme vaccine a “public health fiasco!”.

In 2018, Valneva reported positive phase I interim results for its Lyme vaccine candidate. It is also an OspA vaccine but it includes European Borrelia strains and lacks the region of the proteins that some had attributed to adverse events.

To summarize, as of the end of 2019, that is approximately 20 years after the withdrawal of LYMErix from the market, there is still no vaccine commercially available against LD. Further, those people who were vaccinated with it are probably no longer protected against the disease as the protection diminished over time, albeit at an unknown rate. Enthusiasm for a subsequent product may now be founded more in basic science than in the pharmaceutical industry.

Nonetheless, research is ongoing to develop new vaccines. In addition to the possible avenues to protect against LD such as interruption of transmission and infection at multiple points, current research extends well beyond simple vaccination of humans with emphasis on vaccination against the tick vector itself.

(Note: Vaccines have been formulated and approved for prevention of Lyme disease in dogs. Currently, three Lyme disease vaccines are available: (1) LymeVax, formulated by Fort Dodge Laboratories, contains intact dead spirochetes which expose the host to the organism; (2) Galaxy Lyme, Intervet-Schering-Plough's vaccine, targets proteins OspC and OspA. The OspC antibodies kill any of the bacteria that have not been killed by the OspA antibodies; and (3) Canine Recombinant Lyme, formulated by Merial, generates antibodies against the OspA protein so a tick feeding on a vaccinated dog draws-in blood full of anti-OspA antibodies, which kill the spirochetes in the tick's gut before they are transmitted to the dog.)

Vaccine development considerations

The development of protective vaccines requires the appraisal of multiple factors, both common and pathogen-specific. Given the transmission mode and antigenic variation of Borrelia burgdorferi, the qualities that pertain specifically to this vector-borne infection must be scrutinized. As with many pathogens, the use of whole-cell lysates (that is, the cellular debris and fluid produced by lysis) versus subunit antigens is a safety concern for human use.

A whole-cell lysate vaccine would induce polyclonal antibody responses to multiple antigens that would make differentiation between vaccination and infection difficult. Similarly, conserved antigens amongst spirochetes and other bacteria could confound interpretation of diagnostic tests for Lyme.

On the other hand, subunit vaccines would induce responses to a single or a few antigens, allowing easy distinction from an infection response. The issue would then be how to determine protection and efficacy, and if a serological approach would be required. For Borrelia, which is a pathogen with multiple species and variants found on several continents, will the vaccine protect against other genospecies or variants? Also, given the ability of the tick vector to harbor and transmit multiple pathogens concurrently upon feeding, the protection against possible co-infections must also be taken into account.

Lastly, and of significant importance, what is the duration and type of immunity elicited? The generation of long-lasting B-cell memory responses to Borrelia burgdorferi or tick antigens would be ideal. This would limit the need for multiple booster injections to retain immunity.

Present status of the development of vaccines against LD

Several tick molecules with the potential to serve as vaccines to impair feeding and transmission have been identified in the last decade. The sequenced genome of Ixodes scapularis should enable the development of an effective vaccine against LD.

A tick-based vaccine holds the promise that it might be useful to also simultaneously block the transmission of other tick-borne pathogens. Technologies to genetically manipulate Ixodes scapularis are also coming of age, increasing our understanding of the development, feeding, and pathogen transmission of tick genes. It will also help to prioritize tick antigens for vaccine development.

The Connecticut Agricultural Experiment Station (CAES) and U.S. Biologic, Inc. released the publication of a field trial study showing the effectiveness of an orally-delivered anti-Lyme vaccine that targets the white-footed mouse (the major wildlife source of LD).

The study took place in the residential area of Redding, CT, over a three-year time period and showed substantial decreases in the number of infected mice. One year into the study, test sites that had been treated

with the vaccine showed a 13-times greater decrease in black-legged ticks Ixodes scapularis (the primary vector associated with the spread of disease) infected with Borrelia burgdorferi compared to control sites (i.e., 26% drop versus 2% drop). The vaccine causes the mice to generate antibodies and, therefore, previously infected ticks act as a "xenodiagnostic marker" of vaccine impact, meaning once they ingest the antibodies, while feeding on vaccinated mice, the ticks then become "cleared" of infection.

Reservoir-based approaches in endemic areas – case of rodents

Infectious disease "reservoirs" are what scientists call the places or populations that harbor disease-causing pathogens. For example, certain types of wildlife can be long-term carriers, or hosts, of a disease. Rodents are a major reservoir for LD, so scientists have been looking at ways to prevent them from getting infected with Borrelia burgdorferi. Stopping the bacterial infection in rodents could potentially prevent transmission of the bacteria to the ticks that depend on the rodents in their early life cycle and, therefore, prevent transmission from ticks to humans. The (U.S.) National Institute on Allergies & Infectious Diseases (NIAID) is substantially contributing to these research efforts either directly by its in-house scientists or indirectly by funding other scientists.

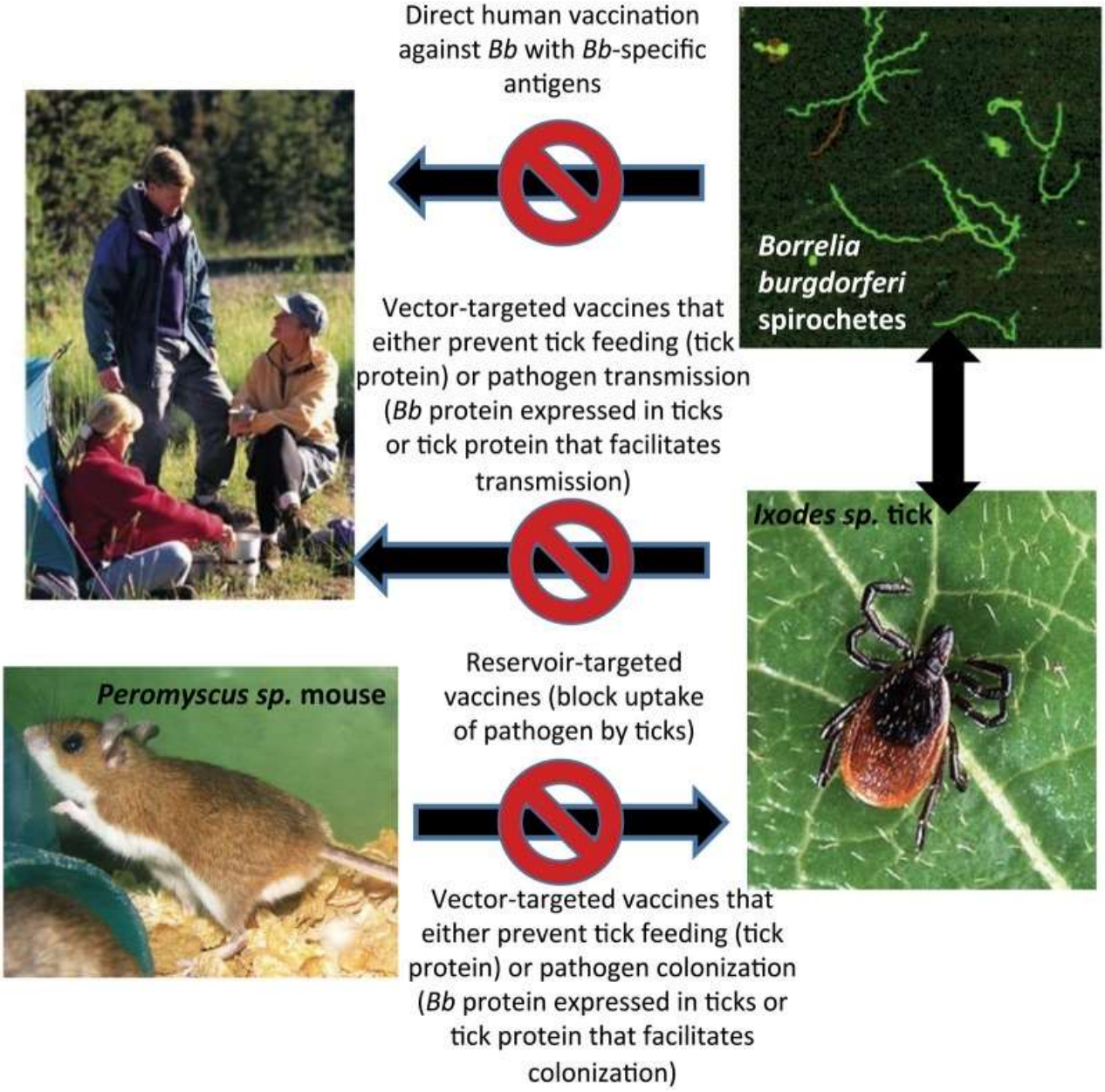
Vaccination of the reservoir hosts and/or humans are not mutually exclusive options. In conjunction with vaccination of humans, targeting the reservoir populations to decrease tick populations and interrupting acquisition or transmission cycles should lead to the control of tick-borne pathogens. Several research groups are investigating the potential of reservoir vaccines to reduce LD in humans focusing on the three types of vaccines discussed below (see Figure 1).

- **Oral-bait vaccines:** These vaccines are aimed at preventing mice from becoming infected, thereby interrupting the transmission cycle. Some groups are field-testing their products with support from CDC&P. Thus, an experimental vaccine-laced bait delivery system has been developed. It was tested on mice which were subsequently exposed to Ixodes ticks carrying multiple strains of Borrelia burgdorferi. Oral vaccination was found to protect 89% of the mice from infection. The blood tests showed their immune systems had created antibodies to the Lyme bacteria.

- **Rice-based vaccine elements:** In a joint study between NIAID, Ventria Bioscience, and CDC &P, rice plants that contain vaccine elements that could eventually be fed to rodent populations were grown, thus blocking the transmission cycle of the disease from rodents to ticks to people. These findings are consistent with the results reported by other investigators.

- **Use of the Vaccinia virus:** In other studies, in a mouse-targeted vaccine using the Vaccinia virus, a single oral dose resulted in strong immune system response and full protection from Borrelia burgdorferi infection. In addition, a significant clearance of Borrelia burgdorferi was observed from infected ticks who fed on vaccinated mice.

The above findings indicate that such a vaccine may effectively reduce the incidence of LD in endemic areas. The pictorial of Figure 1 shows points at which interruption of Borrelia burgdorferi (Bb) transmission to humans can be achieved through vaccination by stopping the Bb spirochetes through direct human vaccination against Bb with Bb-specific antigens. This can be achieved along three routes:



Source:Comstedt P et al (2014)

Figure 1: Points at which interruption of Borrelia burgdorferi transmission to humans can be achieved through vaccination

• **Vector-targeted vaccines by transmission:** They either prevent tick feeding (tick protein) or pathogen transmission (Bb protein expressed in ticks or tick protein that facilitates transmission);

• **Vector-targeted vaccines by colonization:** They either prevent tick feeding (tick protein) or pathogen colonization (Bb protein expressed in ticks or tick protein that facilitates colonization); and

• **Targeting tick saliva:** Multiple research projects are in early-stage discovery and characterization of novel vaccine formulations and targets. They include approaches that target tick saliva that is critical for the transmission of the Lyme bacteria to humans. Tick proteins that facilitate transmission of LD bacteria or that enhance survival of those bacteria in vertebrate hosts have been identified. Studies are ongoing to see if vaccines specifically targeting some of these proteins

• **Reservoir-targeted vaccines:** They block the uptake of pathogens by ticks.

Human vaccine development

Ongoing research activities in human vaccines include the following:

may either be used as a strategy or an "anti-tick vaccine" to be used to prevent disease. Figure 2 is a schematic representation of the dynamic tick saliva. Ixodes scapularis engorges on a vertebrate host skin for 3–7 days, spitting saliva into the host dermis at the bite-site. Salivary composition potentially changes during feeding to confront the different host defense responses.

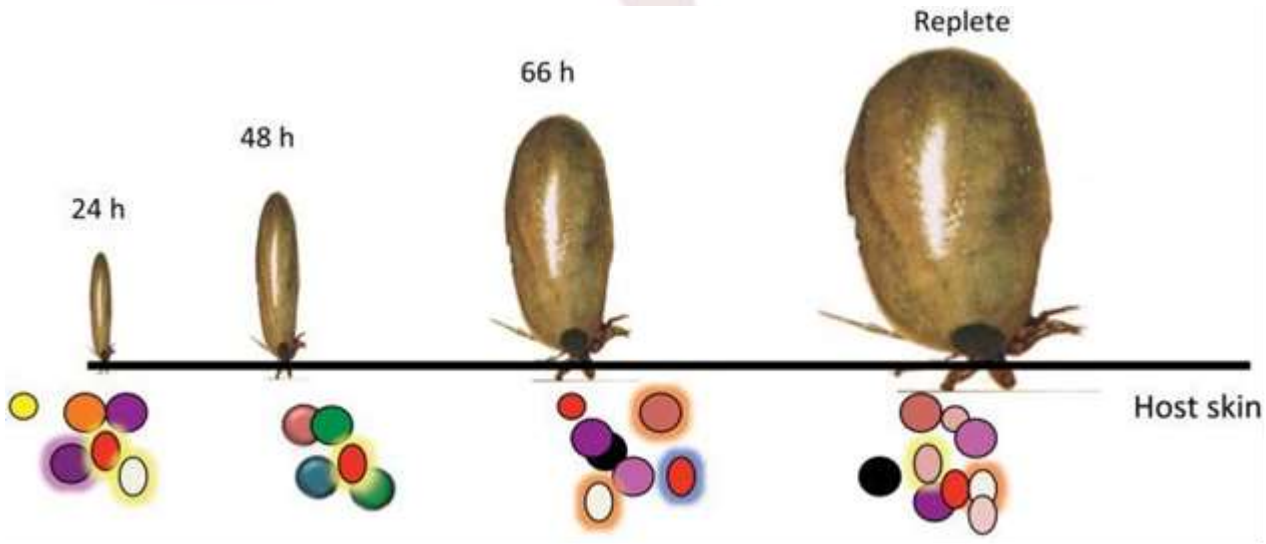


Figure 2: Temporally changing the composition of tick saliva spit into the host's skin

• Modifying the successful canine Lyme disease vaccine; and

• Incorporating antigens against the co-infection anaplasmosis.

Notwithstanding the above and other efforts, a vigorous initiative is still needed for the targeted prevention of tick-borne diseases.

The essential antibody response

Studies in mice have shown that immunity by active immunization to reinfection with Borrelia *burgdorferi* is short-term and declines significantly by 1 year. Reports of human or non-human primate infection with both the LD spirochete and relapsing fever-causing spirochetes also indicate that incidental hosts are likewise susceptible to reinfection. Therefore, immune responses generated during the natural course of infection are insufficient for long-term protection.

By contrast, passive immunization with serum from acute infection in mice or chronic infection in humans has been shown to be protective. In fact, the importance of antibody (AB) responses in controlling these bacterial infections is well-established. These and other findings indicate that the *Borrelia burgdorferi* spirochetes alter antigen expression during infection so as to evade the AB response. Further, they do not elicit effective memory responses to protective antigens (i.e., those that are expressed by all spirochetes and are likely essential for infectivity). Thus, identification of suitable antigens for induction of protective immunity has been a challenge.

Further considerations on Lyme vaccine research and development can be found in the Appendix.

Summary and conclusions

• Lyme disease treatment will vary depending on the stage of the infection (localized, early-disseminated, or late-disseminated) and need to be adjusted depending on a person's age, weight, medical history, underlying health conditions, pregnancy status, or allergies..

• People treated with appropriate antibiotics in the early stages of LD usually recover rapidly and completely. Antibiotics commonly used for oral treatment include amoxicillin, cefuroxime axetil, or doxycycline, The treatment regimens last 2-3 weeks although, in the case of doxycycline. Recent publications suggest greater efficacy for shorter courses.

• For people intolerant of amoxicillin, cefuroxime axetil, and doxycycline, the macrolides azithromycin, clarithromycin, or erythromycin may be used, although they have a lower efficacy and require that patients be closely monitored to ensure that symptoms resolve. Also, people with certain neurological (or cardiac) forms of illness may require intravenous treatment with antibiotics such as ceftriaxone or penicillin.

• For early-disseminated Lyme disease, standard treatment typically lasts only four to six weeks, with extensive treatment widely believed to be unwarranted.

• For late-disseminated Lyme disease, when patients

often relapse (what is known as chronic Lyme disease or Lyme disease complex), the simultaneous presence of multiple different infections in the body seriously complicates any potential treatment and eliminates the possibility of prescription medication as a viable, singular treatment.

• Although most cases of Lyme disease can be cured with a 2- to 4-week course of oral antibiotics, patients can sometimes have symptoms of pain, fatigue, or difficulty thinking that last for more than 6 months after they finish treatment, a condition called post-treatment Lyme disease syndrome. The condition may be caused by one or a combination of autoimmunity, other persistent non-Lyme infection, or even other unrelated causes.

• There is no proven treatment for post-treatment Lyme disease syndrome. Long-term outcomes are no better for patients who received additional prolonged antibiotic treatment than for patients who received placebo. Patients with the syndrome usually get better over time, but it can take many months to feel completely well.

• Long-term antibiotic treatment has been associated with serious, sometimes deadly complications.

• Several placebo-controlled clinical trials have confirmed that, compared to shorter-term antibiotic treatment, there is no evidence of benefit from prolonged antibiotic therapy. Further, it is not an effective strategy for cognitive improvement.

• Tests for the objective monitoring of treatment response are available in two instances: (a) cerebrospinal fluid pleocytosis and (b) electromyography and nerve conduction studies in infections involving the peripheral nervous system.

• Separately and independently, genomic testing may greatly help in prescribing the appropriate personalized treatment and accurately track its progress for each patient.

• Chronic Lyme disease can weaken the immune system, ignite inflammation, squelch energy, provoke pain, and trigger brain fog. It can also generate harmful free radicals, disrupt mitochondria, and overwhelm detoxification pathways.

• Antibiotics are not the best option for chronic Lyme disease because of the incredible defenses presented by Borrelia burgdorferi.. If antibiotics are not the best chronic Lyme disease treatment, a homeopathic treatment option may be available. No less than 21 (may be more) different botanicals have been identified, each one offering unique properties and several of them acting synergistically to help: lower inflammation, reduce joints pain, fight free radical damage, break up biofilm, decrease viral load, regulate the immune system, purge parasites, support detoxification, and combat Lyme bacteria.

• Vaccination against infection is a highly effective means to control the spread of disease in a population. In general, vaccines in common use protect against highly transmissible diseases. Their effectiveness is largely based on the generation of “herd “ immunity.

• A vaccine was marketed in the U.S. between 1998 and 2002 but several factors led to its failure and discontinued manufacturing. Currently, after approximately 20 years thereafter, there is still no vaccine against LD and those people who were vaccinated are probably no longer protected as the protection diminishes over time.

• There are several possible avenues regarding new vaccine development such as interruption of transmission and infection at multiple points, vaccination against the tick vector itself, etc.

• In the development of protective vaccines, the

qualities that pertain specifically to Borrelia burgdorferi vector-borne infection must be scrutinized. How to determine their protection and efficacy remains an issue, and it is not known if a serological approach would be required. Also, the duration and type of immunity elicited are significantly important.

• Ongoing research activities in human vaccine development include targeting tick saliva (critical for transmission to humans), modifying the successful canine Lyme disease vaccine for use in humans, and incorporating antigens against the co-infection anaplasmosis.Notwithstanding these efforts, a vigorous initiative is needed for the targeted prevention of tick-borne diseases.

• Several tick molecules with the potential to serve as vaccines have been identified to impair feeding and transmission. Genome sequencing of the Ixodes scapularis will enable the development of an effective vaccine against Lyme disease.

• Vaccination of the reservoir hosts and/or humans are not mutually exclusive options, and targeting the reservoir populations to decrease tick populations and interrupting acquisition or transmission cycles in conjunction with vaccination of humans should provide the desired goal of controlling tick-borne pathogens.

Appendix
Further considerations on Lyme vaccine research and development

The three main strategies for developing a vaccine are the: (a) transmission-blocking vaccine, (b) targeting the reservoir host, and (c) targeting the tick vector. Each of these is discussed below.

Strategy # 1 - On the transmission-blocking vaccine and its demise

Several antigen subunits of *Borrelia burgdorferi* have been evaluated for their vaccine potential (see Table 5). Except for OspA (the outer surface protein A), all antigens listed are not vaccine candidates on their own. OspA is a lipoprotein whose expression is abundant on in vitro-cultured spirochetes and spirochetes within the tick midgut. It is also quite immunogenic and immunization with OspA provides cross-protection of mice challenged with the North American isolates of *Borrelia burgdorferi*.

***Borrelia burgdorferi* antigen**	**Protective mechanism**	**How tested?**	**Result**	**References**
OspA	Antibody-mediated transmission blocking	o Challenge of mice by infection, tissue transplant, and transmission o Challenge of monkeys by tick transmission	Efficacious. Dependent upon antibody titer	Fikrig *et al.* (1990, 1992) Philipp *et al* (1997) Probert and Lefebvre (1994) Telford *et al* (1995)
OspB	o Antibody mediated o Elicits bactericidal antibodies	Active and passive protective against infection challenges	Potential for strain-dependent efficacy due to truncations of OspB proteins in some strains	Coleman *et al* (1994) Fikrig *et al.* (1993) Probert and Lefebvre (1994) Probert *et al* (1997) Telford *et al* (1993)
OspC	Antibody-mediated within host	Challenge of mice by injection and tick transmission	o Effective but with minimal cross-species protection o Failure to elicit long-term	Gilmore *et al* (1996, 2003) Probert and Lefebvre (1994) Probert *et al* (1997)

			(anamnestic) response	
DbpA	Antibody-mediated within host	Challenge of mice by injection and tick transmission	Protective against injected, but not tick-transmitted infection	Hagman *et al* (2000) Hanson *et al* (1998)
Bbk32 (p35)	Antibody-mediated within host	Passive immunization against infection and tick challenge	Efficacy in combination with DbpA and OspC against challenge by infection and not singly	Brown *et al* (2005) Fikrig *et al.* (1997, 2000)

Source: Adapted from Comstedt P et al (2014)

Key: Osp: Outer surface protein; Bbk: Borrelial lipoprotein; DbpA= DEAD-box RNA.

Table 5: Prospective Lyme vaccine antigens from Borrelia burgdorferi

Some of the positive and negative aspects of the OspA vaccine can be found in Table 6. However, reports emerged suggesting that the vaccine could induce arthritis. This led to anti-vaccine sentiment and class action lawsuits, along with reduced support amongst physicians for the vaccine and eventually enough of a decline in use for its voluntary removal by the manufacturer. Unfortunately, this failure in North America led the leading European prospective Lyme vaccine manufacturer, Pasteur-Merieux-Connaught, to halt its development. This further led to the demise of the OspA vaccine.

Positive	**Negative**
o Blocks transmission o Easier to test for efficacy	Requires maintenance of high antibody titers for efficacy (multiple boosts)
Subunit does not interfere with immunodiagnosis	o Some adverse reactions o Potential for reduced autoimmunity
Targets a reasonably-conserved protein within species	Not effective against other tick-borne diseases

Table 6: Positive and negative characteristics of the OspA vaccine

Strategy # 2 - Targeting the reservoir (mouse) host

Another option for interrupting the transmission of Borrelia burgdorferi to humans is through the vaccination of reservoir hosts. The majority of human infections are transmitted by Ixodes ticks in the nymphal stage so blocking acquisition at the pre-nymphal (larval) stage would be most effective for preventing human infection.

Considerations for a reservoir host vaccine include the antigen type, the route of delivery, the type of delivery system, and the implementation protocol. The OspA antigen is the most efficacious vaccine in animals and the primary choice for the first reservoir-targeting vaccine strategies. It acts by blocking transmission, Vaccination has an impact on the percentage of infected ticks the following year so targeting mouse-dense areas can have a significant impact on carriage, however, the contribution of non-mouse species must also be considered.

The other approach, the baited oral vaccination strategy, achieved protection of mice (89%) and reduction of Borrelia burgdorferi in vector ticks. The advantages of such an approach are its efficacy and the absence of

safety issues.

In a third approach, OspA was delivered by the Vaccinia virus (VV) for several reasons: (1) these viruses have a broad host range; (2) they are stable under the harsh conditions encountered in the digestive tract; (3) they can express proteins at high levels from only a single dose; and (4) their ingestion does not cause disease in wildlife nor is it readily transmissible amongst infected animals. However, the potential to transmit the virus to unwanted recipients remains.

Strategy # 3 - Targeting the tick vector

Historically, vaccines against infectious agents, including Borrelia burgdorferi, have primarily utilized live attenuated pathogens or antigens of the pathogen to induce protective immunity. A potent alternative avenue to protect against arthropod-borne pathogens is targeting the vector itself, be it to eliminate the vector by using chemicals toxic to that vector, by para-transgenic approaches that modify the vectors' ability to transmit pathogens or reproduce, or by use of vaccines targeting vector antigens critical for the vector to feed, reproduce or transmit pathogens. Borrelia burgdorferi is transmitted by five species of Ixodes ticks within the Ixodes ricinus complex: Ixodes scapularis, Ixodes pacificus, and Ixodes cookei in North America, and Ixodes ricinus and Ixodes persulcatus in Europe and Asia, respectively. Additionally, Ixodes scapularis transmits Anaplasma phagocytophilum, Babesia microti, and Powassan virus in North America while Ixodes ricinus and Ixodes persulcatus transmit tick-borne encephalitis virus in Europe and Asia.

Acquired resistance to ticks – just a matter of time

Several decades ago, it was observed that rabbits infested repeatedly with Dermacentor ticks developed a robust immune response resulting in rapid rejection of ticks. This phenomenon of acquired tick resistance has also been noted in various tick-host models. Ixodes scapularis ticks feed successfully on guinea pigs and rabbits at first infestation, but feeding is reduced and ticks fall-off or die within 12–24 hours at subsequent infestations. The hallmark of tick resistance is the swelling and redness at the tick bite site due to cutaneous basophil hypersensitivity, or the rapid recruitment of basophils to the tick bite-site which, followed by their degranulation, effectively thwarts tick feeding, and promotes tick mortality. It is presumed that salivary proteins secreted into the bite site provoke the immune response in the host that recruits basophils to the site. Hence, there is an ongoing interest to exploit the phenomenon of acquired tick resistance to identify tick salivary proteins that are natural targets of host immunity. This would help define salivary protein candidates that might serve as vaccine targets to block tick feeding and Borrelia transmission.

Blocking Borrelia transmission – the real deal

Blocking tick feeding might just be a monumental task, up against the powerful evolutionary measures designed to ensure that the tick saliva is equipped with protein and non-protein biomolecules critical for feeding. But, from a human vaccine perspective, do we really want to block tick feeding? Is it not sufficient that we block pathogen transmission? A vaccine that can effectively block pathogen transmission is undoubtedly the public health goal that is broadly applicable to the murine reservoir host and to humans. Whereas the manufacture of the first such vaccine (OspA) has been discontinued, a safe and effective vaccine against LD has since then remained an unmet need.

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