Journal of Pre-Clinical and Clinical Research 2024, Vol 18, No 3, 276-281
www.jpccr.eu

REVIEW ARTICLE

Current methods of treatment and prevention of Lyme borreliosis – literature review

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Pyc G, Kowalewski J, Dąbrowska A, Bęben D, Dudzik M, Majewski K, Pakos K, Durmała K, Sielicka U, Mączka J. Current methods of treatment and prevention of Lyme borreliosis – literature review. J Pre-Clin Clin Res. 2024; 18(3): 276–281. doi: 10.26444/jpccr/192029

Abstract

Introduction and Objective. Lyme borreliosis is a disease caused by infection with spirochetes of the genus Borrelia through the transmission of these bacteria by Ixodes ticks. The bacteria spread from the bite site through the bloodstream to distant organs, causing specific symptoms. A characteristic erythema migrans may occur at the site of the bite. The aim of the study is to summarize current guidelines and review articles on the treatment and prevention of this disease.

Review Methods. Articles were searched by combinations of of key words, such as: Lyme disease, treatment, prevention, in PubMed databases. Scientific articles covering the period 2016–2024 account for 92% of all references. Guidelines from European and American societies of epidemiologists, infectious disease physicians, neurologists, and studies from specialized research centres, including meta-analyses, double-blind randomized trials and case reports were considered. Studies from inexperienced centres with outdated studies that do not follow the latest guidelines were rejected.

Brief description of the state of knowledge. Current treatments for Lyme borreliosis are based on antibiotic therapy for clinical symptoms, and symptomatic treatment in the absence of response to antibiotic therapy. In specific prophylaxis, an antibiotic is recommended post-exposure in some cases. For non-specific prophylaxis, it is recommended to follow the rules for preventing tick bite.

Summary. Currently, the treatment of Lyme disease is mainly based on antibiotic therapy. Depending on the clinical manifestation, treatment is based on different antibiotics with a treatment duration of no more than 28 days. Adherence to prophylactic recommendations helps reduce the risk of infection. The development of a human vaccine is still under intensive development.

Key words

treatment, Lyme disease, prevention, Borrelia burgdorferi

INTRODUCTION AND OBJECTIVE

Lyme borreliosis is a zoonotic disease caused by gram-negative *Borrelia spirochetes*. In European countries, the disease is most often caused by *Borrelia afzelii* or *Borrelia garinii* species, less often by *Borrelia burgdorferi*. On the North American continent, the most common genospecies causing the disease is *Borrelia burgdorferi* [1], while in Europe, the disease is mainly caused by the bite of *Ixodes ricinus* and *Ixodes persulcatus* ticks. In the United States, *Ixodes scapularis* and *Ixodes pacificus* are the main cause. The disease is most common in North America, Cntral and Northern Europe and Northern Asia [2]. Transmission of the bacteria by an infected tick varies depending on the species of bacteria, as well as the tick. In the case of *Borrelia afzelii* which are transmitted by *Ixodes ricinus* ticks, infection can occur as early as less than 24 hours after the bite. Transmission of infection after 36 hours is more common for *Borrelia burgdorferi* carried by *Ixodes scapularis* ticks [3]. A large proportion of infections are transmitted by tick nymphs, which is due to the fact that they are smaller than mature individuals and are more difficult to spot on the skin surface [3]. The risk of transmission increases with the length of time an infected tick is on the skin surface. The primary lesion, erythema migrans, appears at the site of a tick bite usually within 3–30 days. Tick bites most often occur in late spring and early summer due to the increased number of ticks and more frequent activity of people outdoors [3], and most commonly found in forests, parks, meadows in both urban and suburban areas [4].

The aim of the study is to summarize current guidelines

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Received: 05.06.2024; accepted: 05.08.2024; first published: 09.09.2024

and review articles on the treatment and prevention of the disease. A summary of the opinions of many scientific societies will help to present the developed standards and synthesize knowledge on the prevention of Lyme disease.

REVIEW METHODS

Articles were searched by a combinations of key words, such as Lyme disease, treatment, prevention, in PubMed databases. Scientific articles covering the period 2016–2024 account for 92% of all references. Guidelines from European and American societies of epidemiologists, infectious disease physicians, neurologists, and studies from specialized research centres including meta-analyses, double-blind randomized trials and case reports, were taken into consideration. Studies from inexperienced centres with outdated studies that do not follow the latest guidelines were rejected.

STATE OF KNOWLEDGE

Risk factors for infection. Factors that increase the risk of infection include occupations (forest workers, hunters), social behaviour (being in forests in endemic areas without proper preparation, pilgrims, gardening) [5], prolonged time the tick stays on the skin surface, attempts to squeeze or lubricate ticks, as this increases the risk of tick vomiting and entry of bacteria and viruses into the human body [3].

Clinical picture of Lyme Lyme disease. Lyme disease can be divided into two forms: early and late, with the early form divided into limited and disseminated. The most common early limited form and the first symptom of Lyme Lyme disease is erythema migrans. Migratory erythema is a gradually enlarging ring-shaped lesion on the skin, with central translucency and a red border. The lesion appears between 3–30 days after a tick bite, usually after 7 days [6]. In addition, the early limited form includes flu-like symptoms and, less commonly, a Lyme lymphocytoma in the form of a non-painful nodule in the auricular or scrotal region. Symptoms of the early disseminated stage that develop in a few weeks to a few months include: arthritis, myocarditis and neuroborreliosis (in the form of lymphocytic meningitis or cranial neuritis). The late form includes: chronic atrophic dermatitis, chronic arthritis, and rarely, chronic neuroborreliosis [7].

Treatment of Lyme disease. Treatment of Lyme disease is based on specific antibiotic therapy depending on the form of the disease, the organs involved and the age of the patient [7]. Very broad-spectrum antibiotics such as fluoroquinolones or aminoglycosides are not recommended. The duration of antibiotic treatment should usually be limited to 28 days, as longer therapy is not beneficial and may only increase the risk of side-effects [8, 11]. Non-steroidal anti-inflammatory drugs are recommended for flu-like symptoms, and in the case of large amounts of joint effusion, a puncture can be performed for decompression, which will reduce the pain experienced [9, 11].

Erythema migrans. The appearance of erythema migrans after a tick bite undoubtedly requires treatment without expanding the diagnosis. Erythema migrans appears within 30 days after the bite, it is therefore recommended that patients observe the site of the tick bite during this time. The National Institute for Health and Clinical Excellence (NICE) guidelines recommend doxycycline as the treatment of choice for 21 days at a dose of 200 mg once a day, or in two doses of 100 mg each (Tab. 1) [8]. In contrast, guidelines from the Infectious Diseases Society of America (IDSA), the American Academy of Neurology (AAN) and the American College of Rheumatology (ACR), indicate doxycycline for 10 days or the use of amoxicillin 500 mg three times a day for 14 days, or cefuroxime axetil 500 mg twice daily as first-line treatment [9]. Polish guidelines of the Society of Epidemiologists and Physicians of Infectious Diseases (PTEiLChZ) recommend doxycycline used from 7–21 days or amoxicillin or axetil cefuroxime for 14–21 days [10]. The lower number of days of doxycycline treatment than in other societies is due to the fact that one study showed that 7-day antibiotic therapy had comparable cure rates to 2-week therapy, and allowed for a reduction in time exposure to doxycycline [11]. Spanish societies, such as the Society of Infectious Diseases and Clinical Microbiology (SEIMC), Society of Neurology (SEN), Society of Immunology (SEI), Spanish Society of Paediatric Infectology (SEIP), Society of Rheumatology (SER), and the Academy of Dermatology and Venerology (AEDV), jointly recommend that doxycycline be used first for 10–21 days. As a second choice, they recommend amoxicillin or cefuroxime axetil for 14–21 days [12].

Recent reports clearly show a trend toward shorter periods of antibiotic therapy showing similar cure rates for patients with both long and short therapy. This is important in the context of the shortest effective treatment period, antibiotic

Table 1. Treatment of erythema migrans according to the guidelines of international societies

	PTEiLChZ [10]	IDSA/ANN/ACR [9]	NICE [8]	SEIMC/SEN/SEI/SEIP/SER/AEDV [12]
First-choice treatment	1. Doxycycline for 7–21 days, twice daily 100 mg or once daily 200 mg. 2. Amoxicillin for 14–21 days, 3 times daily 500 mg. 3. Cefuroxime axetil for 14–21 days, twice daily 500 mg.	1. Doxycycline for 10 days, twice daily at a dose of 100 mg or once daily at a dose of 200 mg. 2. Amoxicillin for 14 days, 3 times daily 500 mg. 3. Cefuroxime axetil for 14 days, twice daily 500 mg 4. Azithromycin for 5–10 days, once daily 500 mg	Doxycycline for 21 days, twice daily at a dose of 100 mg, or once daily at a dose of 200 mg.	Doxycycline for 10–21 days, twice daily at a dose of 100 mg, or once daily at a dose of 200 mg.
Second-choice treatment	1. Azithromycin for 5–10 days, once daily 500 mg		1. Amoxicillin for 21 days, 3 times daily 500 mg. 2. Azithromycin for 17 days, once daily 500 mg.	3. Amoxicillin for 14–21 days, 3 times daily 500 mg. 4. Cefuroxime axetil for 14–21 days, twice daily 500 mg. 5. Azithromycin for 5–10 days, once daily 500 mg

Table 2. Treatment of Borrelial lymphocytoma according to the guidelines of international societies

	PTEiLChZ [10]	IDSA/ANN/ACR [9]
First-choice treatment	1. Doxycycline for 14–21 days, twice daily 100 mg or 1 time daily 200 mg. 2. Amoxicillin for 14–21 days, 3 times daily 500 mg. 3. Cefuroxime axetil for 14–21 days, twice daily 500 mg	1. Doxycycline for 14 days, 2 times daily 100 mg or once daily 200 mg 2. Amoxicillin for 14 days, 3 times daily 500 mg. 3. Cefuroxime axetil for 14 days, twice daily 500 mg

Table 3. Treatment of Lyme arthritis according to guidelines of international societies

	PTEiLChZ [10]	IDSA/ANN/ACR [9]	NICE [8]	SEIMC/SEN/SEI/SEIP/SER/AEDV [12]
Treatment of the first episode	1. Doxycycline for 28 days, twice daily 100 mg or once daily 200 mg. 2. Amoxicillin for 28 days, 3 times daily 500 mg. 3. Cefuroxime axetil for 28 days, twice daily 500 mg.	1. Doxycycline for 28 days, twice daily 100 mg, or once daily 200 mg. 2. Amoxicillin for 28 days, 3 times daily 500 mg. 3. Cefuroxime axetil for 28 days, twice daily 500 mg.	1. Doxycycline for 28 days, twice daily 100 mg, or once daily 200 mg.	1. Doxycycline for 28 days, twice daily 100 mg, or once daily 200 mg. 2. Amoxicillin for 28 days, 3 times daily 500 mg. 3. Ceftriaxone for 28 days, once daily 2 g intravenously.
Treatment of recurrence	1. Ceftriaxone for 14–28 days, once daily 2 g intravenously.	1. Doxycycline for 28 days, twice daily 100 mg or once daily 200 mg. 2. Amoxicillin for 28 days, 3 times daily 500 mg. 3. Cefuroxime axetil for 28 days, twice daily 500 mg 4. Ceftriaxone for 14–28 days, once daily 2 g intravenously.	1. Amoxicillin for 28 days, 3 times daily 500 mg. 2. Ceftriaxone for 28 days, once daily 2 g intravenously.	

resistance and adverse effects of prolonged antibiotic exposure in patients [10,13]. In the case of contraindications to both doxycycline and amoxicillin or cefuroxime, azithromycin 500 mg once a day for 5–10 days is recommended [9, 10, 14].

Lymphocytoma of Lyme disease. Lymphocytoma borreliosis usually presents as a purplish nodule which most often appears within 2–8 weeks after infection, and more often affects children [15]. In adults, it most often occurs in the nipple, earlobe, scrotum, or less frequently in other locations [16]. In the case of a positive test for specific IgG or IgM antibodies, antibiotic-based treatment is used. The PTEiLChZ guidelines recommend doxycycline or amoxicillin or cefuroxime axetil for 14–21 days (Tab. 2) [10]. IDSA/ANN/ACR recommend using these antibiotics for 14 days [9].

Lyme arthritis. Lyme arthritis is a disease that usually affects the large joints, affecting mainly the knees, shoulders, elbows and ankle joints [17]. It appears after a few weeks and can last up to several months, and sometimes, despite treatment, progresses to persistent arthritis. There are periods of exacerbations which become increasingly shorter with the duration of the disease. During the course of the disease, swelling and pain occur in the affected joints [18]. PTEiLChZ, Spanish and US guidelines recommend doxycycline, amoxicillin or cefuroxime axetil for 4 weeks at the first episode (Tab. 3) [9, 10, 12]. UK NICE also recommends 4 weeks of therapy, but recommends doxycycline as the drug of first choice [8]. For recurrent arthritis, intravenous ceftriaxone is recommended for 14–28 days [10], or repeating the original antibiotic therapy [9].

Lyme carditis. Lyme carditis in the course of Lyme disease occurs in about 0.5–5% of patients. It belongs to the early disseminated stage and usually develops within 3 weeks, and can appear even after several months [19]. The main clinical manifestation in patients with myocarditis is atrioventricular blocks, usually of the 1st or 2nd degree. Up to 67% may subsequently develop complete heart block and need pacemaker support [20]. Less commonly, cardiac involvement by infection can manifest as endocarditis, pericarditis, myocardial infarction, atrial and ventricular arrhythmias, dilated cardiomyopathy or heart failure. It is recommended that Lyme disease be ruled out in young patients before permanent pacemaker placement due to the fact that these patients, after causal treatment, i.e. appropriate antibiotic therapy, no longer have symptoms of conduction disturbances and do not require pacing [21]. After excluding other cardiac causes of myocarditis and confirming the presence of specific antibodies, antibiotic therapy is recommended (Tab. 4). Polish guidelines recommend antibiotics (doxycycline or amoxicillin or cefuroxime or intravenous ceftriaxone) for 14–21 days. As a second-line treatment, intravenous cefotaxime or penicillin G can also be used for 14–21 days [10]. NICE guidelines recommend that haemodynamically stable patients with myocarditis should be treated with doxycycline for 21 days, and haemodynamically unstable patients should be treated with intravenous ceftriaxone for 21 days [8].

Acrodermatitis chronica atrophicans. This is among the late manifestations of Lyme disease and can appear from several months to even several years after infection. It initially manifests itself by the presence of bluish-red lesions on the surface of the extremities, together with swelling and pain. If left untreated, it progresses to fibrosis and skin atrophy [22].

The clinical features of peripheral neuropathy are often associated symptoms. The presence of specific IgG class antibodies and a positive histopathological examination of the altered skin, or the finding of Borrelia genetic material in a skin biopsy, are indications for initiating treatment [23]. It is recommended that antibiotic therapy should last 21–28 days (Tab. 5). The drug of choice may be doxycycline or amoxicillin or cefuroxime [9, 10]. In contrast, UK guidelines

Table 4. Treatment of Lyme carditis according to the guidelines of international societies

	PTEiLChZ [10]	IDSA/ANN/ACR [9]	NICE [8]
First-choice treatment	1. Doxycycline for 14–21 days, twice daily 100 mg, or once daily 200 mg. 2. Amoxicillin for 14–21 days, 3 times daily 500 mg. 3. Cefuroxime axetil for 14–21 days, twice daily 500 mg. 4. Ceftriaxone for 14–21 days, once daily 2 g intravenously.	1. Doxycycline for 14–21 days, twice daily 100 mg, or once daily 200 mg. 2. Amoxicillin for 14–21 days, 3 times daily 500 mg. 3. Cefuroxime axetil for 14–21 days, twice daily 500 mg. 4. Azithromycin for 14–21 days, once daily 500 mg. 5. In hospitalized patients: Ceftriaxone for 14–21 days, once daily 2 g intravenously.	1. Hemodynamically stable patients: Doxycycline for 21 days, twice daily at 100 mg, or once daily at 200 mg. 2. Haemodynamically unstable patients: Ceftriaxone for 21 days, once daily 2 g intravenously.
Second-choice treatment	1. Cefotaxime for 14–21 days, 3 times daily 2 g intravenously.. 2. Penicillin G for 14–21 days, 18–24 million units per day divided in 6 doses intravenously.		

Table 5. Treatment of Acrodermatitis chronica atrophicans according to guidelines of international societies

	PTEiLChZ [10]	IDSA/ANN/ACR [9]	NICE [8]
First-choice treatment	1. Doxycycline for 21–28 days, twice daily 100 mg, or once daily 200 mg. 2. Amoxicillin for 21–28 days, 3 times daily 500 mg. 3. Cefuroxime axetil for 21–28 days, twice daily 500 mg.	1. Doxycycline for 21–28 days, twice daily 100 mg, or once daily 200 mg. 2. Amoxicillin for 21–28 days, 3 times daily 500 mg. 3. Cefuroxime axetil for 21–28 days, twice daily 500 mg.	1. Doxycycline for 28 days, twice daily 100 mg, or once daily 200 mg.
Second-choice treatment			1. Amoxicillin for 21–28 days, 500 mg 3 times daily. 2. Ceftriaxone for 28 days, once daily 2 g intravenously.

Table 6. Treatment of various forms of neuroborreliosis according to guidelines of international societies

	PTEiLChZ [10]	IDSA/ANN/ACR [9]	NICE [8]	SEIMC/SEN/SEI/SEIP/SER/AEDV [12]
First-choice treatment	Meningitis or radiculopathy: 1. Doxycycline for 14–21 days, twice daily 100 mg, or once daily 200 mg. 2. Cefotaxime for 14–21 days, 2 g intravenously 3 times daily. 3. Ceftriaxone for 14–21 days, once daily 2 g intravenously. Cranial nerve paralysis: 1. Doxycycline for 14–21 days, twice daily 100 mg, or once daily 200 mg.	Meningitis or radiculopathy: 1. Doxycycline for 14–21 days, twice daily at 100 mg, or once daily at 200 mg. 2. Ceftriaxone for 14–21 days, once daily 2 g intravenously. Cranial nerve paralysis: 1. Doxycycline for 14–21 days, twice daily at a dose of 100 mg or, once daily 200 mg.	Central nervous system symptoms: 1. Ceftriaxone for 21 days, once daily 2 g intravenously Symptoms from the peripheral nervous system or cranial nerves: 1. Doxycycline for 21 days, twice daily 100 mg or once daily 200 mg.	Early neuroborreliosis: 1. Doxycycline for 14–28 days, twice daily 100 mg, or once daily at 200 mg. 2. Cefotaxime for 14–28 days, 3 times daily 2 g intravenously. 3. Ceftriaxone for 14–28 days, once daily 2 g intravenously. 4. Doxycycline for 14–28 days, twice daily 100 mg, or once daily 200 mg. Late neuroborreliosis: 1. Doxycycline for 14–21 days, twice daily at a dose of 100 mg, or once daily 200 mg. 2. Ceftriaxone for 14–21 days, once daily 2 g intravenously.

recommend doxycycline for 4 weeks as first-line treatment. This can be followed by oral amoxicillin or intravenous ceftriaxone for 28 days [8].

Neuroborreliosis. A broad term that encompasses nervous system involvement in the course of Lyme Lyme disease. Neuroborreliosis occurs in the vast majority of early forms appearing up to several months after infection. Migratory erythema co-occurs in about 40% of patients. Typical clinical conditions in early neuroborreliosis are meningitis, cranial nerve palsy and spinal roots [24]. Late neuroborreliosis can manifest as inflammation of the brain and spinal cord, with spastic symptoms, mobility and micturition disorders [25].

The most common set of symptoms are the Garin, Bujadoux and Bannwarth syndrome, which consists of meningitis, cranial nerve palsy and root syndrome [26]. When cranial nerves are involved, all of them – with the exception of the olfactory nerve – may be paralyzed. Most often, the facial nerve is paralyzed unilaterally and somewhat less often bilaterally. The symptoms of paralysis usually resolve within 8 weeks, [27, 28]. When the central nervous system is involved, and causes other than Lyme disease are excluded, the presence of intrathecal synthesis of specific antibodies is required and the demonstration of pleocytosis in the cerebrospinal fluid is helpful. On the other hand, for symptoms from the peripheral nervous system after excluding other causes, the presence of specific antibodies in serum is required [24,29]. Confirmed neuroborreliosis requires antibiotic treatment, depending on its clinical form (Tab. 6).

For cranial nerve palsy, doxycycline is usually recommended for 14–21 days [8, 9, 10]. Meningitis most commonly requires doxycycline or ceftriaxone intravenously for 14–21 days [8,9,10]. In some cases, penicillin G can be used as 2nd-line treatment [8, 10].

PROPHYLAXIS

Specific prophylaxis. IDSA, AAN and ACR guidelines recommend that multiple tick bites in people outside endemic areas be treated with a single dose of doxycycline 200 mg orally within 72 hours of tick exposure [9, 30]. An open-label, randomized, controlled trial found that patients

administered a single dose of 200 mg of doxycycline within 72 hours after removing a tick from their skin, had a 67% lower risk of contracting Lyme disease compared to patients who did not take the antibiotic [31]. In contrast, a meta-analysis of 4 studies showed that a single dose of doxycycline within 72 hours protects against Lyme disease in 87% of cases [32].

Currently, there are no registered vaccines to protect against contracting Lyme disease. Research is being conducted on proteins produced by the Borrelia spirochetes which are expected to help in the future development of vaccines [33]. The difficulty in developing a good vaccine is the diversity of Borrelia strains in different regions of the world, making it necessary for vaccines to have a broad list of antigens on which to base further immune action [34]. VLA15 is a vaccine based on the recombinant outer surface protein (OspA) which, by its promising results in mice, may in the future present a real chance in the fight against Lyme disease in humans. Currently, this vaccine is in clinical trials with humans [35]. Another vaccine that also offers hope after its optimistic results on mice is the mRNA vaccine encoding the OspA protein. This has shown a large immune response after just one administration, and may be the subject of human trials in the near future [36].

Non-specific prophylaxis. Individuals who have increased exposure to ticks can themselves influence risk reduction by following certain rules. If there is no way to avoid situations of increased exposure to ticks, it is advisable to wear light-coloured clothing that covers exposed areas. It is also recommended to use repellents with permethrin, icardin, diethyl-meta-toluamide (DEET) and eucalyptus oil. Another important element of prophylaxis is to carefully inspect the skin after returning from areas where there are increased numbers of ticks. If a tick is found on the surface of the skin, it is recommended that it be removed as soon as possible by using tweezers. Lubricating with greasy creams, burning or squeezing the tick is not recommended as this increases the risk of infection. The site after tick removal should be disinfected [9, 37].

Testing ticks for Borrelia spirochete infection is also not recommended. A positive tick infection result is not conclusive of infection in a person who has been bitten. Tick testing cannot have a binding effect on the decision to treat Lyme disease, nor does it have diagnostic significance [38].

SUMMARY

Advances regarding the understanding of the immunological basis of the infection, as well as the expansion and standardization of diagnostics, have a direct impact on the quality and rationality of treatment. The current study has collected the latest information and guidelines of societies that summarize the most recent developments and standards evolved for the treatment of Lyme disease.

The basis of Lyme disease therapy is antibiotic therapy which, as a causal treatment, undoubtedly brings many benefits. The choice of antibiotic and the duration of its use depends on the clinical manifestation of Lyme borreliosis. Summarizing the various guidelines, slight differences can be noted in the choice of antibiotic and duration of its use.

The right choice of antibiotic and the length of its use allows for a cure in very many cases, although doctors need to be aware of when antibiotic therapy should be used, and when only detailed observation of the tick bite site and the patient's symptoms is sufficient. Each patient should be treated individually and observed for worrisome symptoms. In cases that require antibiotic therapy, the patient should be ordered to take specific antibiotics immediately. However, it is worth noting that current trends in the guidelines limit the situations in which antibiotic therapy is necessary and reduce its duration. Public concern about tick bites can lead to a trend of over-prescribing antibiotic therapy, which has negative consequences for the environment, as well as the person who receives it. Overuse of antibiotics leads to increasing antibiotic resistance among pathogens, and often adversely affects the intestinal microflora, causing adverse reactions to various antibiotics.

In the prevention of Lyme disease, attention continues to be paid to adherence to the recommendations of dressing while in environments with an increased risk of infection, the use of repellents and observation of the site after a tick bite.

Research is being conducted on the development of vaccines that in the future may form the basis of the fight to reduce the occurrence of Lyme disease. Promising preliminary results indicate the need to expand research on new preparations that may form the basis of prevention in the near future.

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