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Diagnosis and treatment of "chronic Lyme": primum non nocere. A review

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Abstract

BACKGROUND: Approximately 10% of patients experience prolonged symptoms after Lyme disease. PTLDS (post treatment Lyme disease syndrome) is a controversial topic. It has been described as a source of overdiagnostic and off-label treatment. The objective of this work was to describe, in the context of the PTLDS, the diagnostic errors and adverse effects of drugs used outside the recommendations.

METHODS: systematic review of the literature according to PRISMA criteria, including randomized clinical trials (RCT), observational studies, and case reports addressing diagnostic errors and adverse events published between January 2010 and November 2020 in English or French.

RESULTS: 16 studies were included: 1 RCT, 7 observational studies and 8 case reports. In the 5 observational studies, overdiagnosis rates were very high, ranging from 80% to 100%. The new diagnoses were often psychiatric, rheumatological and neurological. Disorders with somatic symptoms were often cited. Diagnostic delays were identified for cancers and frontoparietal dementia. In the RCT and observational studies, prolonged anti-infective treatments were also responsible for adverse events, with emergency room visits and/or hospitalization. The most common adverse events were diarrhea, sometimes with *Clostridium difficile* colitis, electrolyte abnormalities, sepsis, bacterial and fungal infections, and anaphylactic reactions.

CONCLUSION: This review informs patients and physicians of the risks of prolonged anti-infective treatment that has not been proven to be beneficial. It does not seem ethical to offer such treatments to patients given the imperative of the "*primum non nocere*" principle of non-maleficence.

Background

Approximately 10% of patients experience prolonged symptoms (asthenia, diffuse pain, cognitive problems, etc.), after Lyme disease [1, 2]. These patients with post treatment Lyme disease syndrome (PTLDS) often experience a feeling of non-recognition and abandonment by physicians [3–5]. Faced with these feelings, they sometimes consult informally specialized doctors, who recommend the use of uncertified tests in private laboratories, and unapproved anti-infective drugs [6–8].

These off-label management issues raise the question of misdiagnosis and overdiagnosis of Lyme borreliosis (LB). In 2018, a patient with lupus attributed her symptoms to LB on the basis of her findings on the internet. She was given long-term tetracycline treatment. She died of multi-organ failure [9]. These misdiagnoses could affect 9 out of 10 patients attributing their symptoms to LB [10–13]. Such overdiagnosis prompted the American College of Rheumatology (ACR) to include LB in the "Top five list" as part of the "Choosing Wisely" campaign [14].

These treatments also raise the question of the benefit-risk balance. Several randomized clinical trials have tested various anti-infectives in PTLDS. These studies did not show evidence of benefit from the

treatments [15–19]. In 2000, Patel described the case of a 30-year-old woman who died of nosocomial sepsis with a catheter that had been used for 27 months for treatment with ceftriaxone [20].

The objective of this review was to describe, in the context of PTLDS, the diagnostic errors and adverse effects of drugs used outside the guidelines. The aim was to inform patients of the risks and to put the ethical principle of non-maleficence back at the center decisions.

Methods

A review of the literature was conducted according to the PRISMA criteria.

Inclusion criteria

Randomized clinical trials (RCTs), observational studies and case reports addressing diagnostic errors and adverse drug reactions in PTLDS published between January 1, 2010, and November 5, 2020, in French or English, were included.

Exclusion criteria

Position papers or recommendations for PTLDS were excluded.

Search equations and databases

With the help of a librarian, the Medline and Cochrane Library databases were searched with the following search equation: "Lyme disease" [MeSHTerms] OR "Lyme neuroborreliosis" [MeSHTerms] OR "erythema chronicum migrans" [MeSHTerms] OR "post Lyme disease syndrome" [MeSHTerms]) AND "inappropriate prescribing" [MeSHTerms] OR "diagnostic errors" [MeSHTerms] OR " [MeSHTerms] OR "adverse effects" [SH] OR "poisoning" [MeSHTerms].

Selection of articles

The articles were selected using a quadruple reading process by SP, JD, CP and XG on the basis of the titles and abstracts of the different articles (Fig. 1).

Data analysis

For each selected article, the name of the lead author, the country, the date of publication, the method and the diagnostic errors and adverse effects of the drugs used were described.

Results

Of the 561 articles identified, 15 were included: 1 randomized clinical trial (RCT) [16], 7 observational studies [11–13, 21–24] and 7 case reports [25–31] (Figure). Tables 1 and 2 detail the lead author, year of publication, country of research, population, and diagnostic error-delay and adverse events.

Table 1
Observational and case report studies related to overdiagnosis

Type of study	Lead author Year Reference	Country	Population	Overdiagnosis
Observational studies	Haddad E (2019) [11]	France	301 patients PTLDS	Overdiagnosis = 80.7% (n = 243) differential diagnosis: psychiatric (depression, post-traumatic stress, burnout syndromes, etc.) 25.2% (n = 76) rheumatological (osteoarthritis, scoliosis) 15.9% (n = 48) neurological (Parkinson's and amyotrophic lateral sclerosis)12.3% (n = 37) OSA 4.9% (n = 15) No diagnosis 6.6% (n = 20)
	Haddad E (2019) [12]	France	4 weeks 1000 patients 3 centers	Overdiagnosis: 90.4, 88, 85% differential diagnosis: psychiatric 25, 19 and 13% rheumatological 16, 14 and 32% neurological 12, 6 and 5% no diagnosis 6, 29 and 26%
	Itani O (2020) [13]	France	Paris, Besançon, Nancy 15 patients 6 months	Overdiagnosis: 100% (n = 15) differential diagnosis: psychiatric FSS 60% (n =9) neurological 20% (n =3), 1 OSA
	Kobayashi Y (2019) [22]	United States	1261 patients	Overdiagnosis: 84.1% (n = 1061)

OSA: Obstructive Sleep Apnea ; ABX: antibiotics ; LB: Lyme borreliosis ; FSS: functional somatic syndrome

Type of study	Lead author Year Reference	Country	Population	Overdiagnosis
	Peri F (2019) [24]	Italy	7 children	Overdiagnosis: 100% (n = 7) differential diagnosis: psychiatric (n = 6) viral infection (n = 1-
Case report	Andany N (2015) [7]	United States	a 35-year-old man with chronic fatigue > 1 year	Public Serology LB < 0 Private Serology > 0
	Nelson C (2015) [25]	United States	3 patients PTLDS ATX treatment (tetracyclines, clarithromycin and hydroxychloroquine)	diagnostic delay pituitary tumor Hodgkin lymphoma stage 4 lung cancer
	Di Battista ME (2018) [26]	Italy	61-year-old patient: doxycycline (21 days and 14 days)	diagnostic delay (4 years) frontotemporal dementia

OSA: Obstructive Sleep Apnea ; ABX: antibiotics ; LB: Lyme borreliosis ; FSS: functional somatic syndrome

Table 2
RCTs, observational studies and case reports related to adverse events (AEs)

RCT	**Krupp LB (2003) [16]**	**United States**	**55 PTLDS patients** **28 ceftriaxone IV** **27 placebo** **6 months**	**AEs: diarrhea** **ceftriaxone group 43%** **placebo group 25%** **Hospitalizations: 4** **ceftriaxone group: 1 anaphylaxis, minor anaphylactic reactions: 2** **placebo group: 3 IV catheter sepsis**
Observational studies	Itani O (2020) [13]	France	15 patients On average 6.8 ABX / 476 days	AEs: 27% (n = 4) 1 *clostridium difficile* colitis 3 fungal infections
	Trautmann A (2020) [21]	France	16 Disulfiram patients	Various and moderate AEs: 81.2% (n = 13)
	Goodlet KJ (2018) [23]	United States	3127 patients Group 1: 1102 ABX *per os* Group 2: 150 IV Groupe 3: 1875 placebo	AEs: group 1: 18.7%, group 2: 16.8%, group 3: 13.4% Infections 20.4%, gastrointestinal disorders 6.2%, electrolyte disorders 2.6% Hospitalizations: group 1: 2.2%, group 2: 7.3%, group 3: 0.9% Emergencies: group 1: 3.4%, group 2: 11.3%, group 3: 1.9%
Cases report	Johnstone T (2018) [27]	Australia	41-year-old woman Glutathion + Phosphatidylcholine	AEs: bacterial septicemia then *Clostridium Difficile* colitis

Randomized Clinical Trial: RCT ; intravenous (IV) : antibiotics: ABX

RCT	**Krupp LB (2003) [16]**	**United States**	**55 PTLDS patients** **28 ceftriaxone IV** **27 placebo** **6 months**	**AEs: diarrhea** **ceftriaxone group 43%** **placebo group 25%** **Hospitalizations: 4** **ceftriaxone group: 1 anaphylaxis, minor anaphylactic reactions: 2** **placebo group: 3 IV catheter sepsis**
	Issacs D (2016) [28]	Australia	15-year-old woman Hyperthermia and ABX IV	AEs: severe dehydration due to *Clostridium Difficile* diarrhea
	Shelton A (2019) [29]	United States	32-year-old woman ABX IV (rifabutin, metronidazole, ivermectin, and pyrimethamine) then ABX *per os* (meropenem, clindamycin, tigecycline, and ciprofloxacin)	AEs: *Mycobacterium goodii* multifocal pneumonia on central venous catheter
	Marcks CM (2016) [30]	United States	45-year-old woman ABX 3 months *per os* (doxycycline, minocycline and trimethoprim-sulfamethoxazole	AEs: DRESS Syndrome
	De Wilde M (2017) [31]	Belgium	76-year-old woman ceftriaxone IV	AEs: drug-induced immunohemolytic anemia
Randomized Clinical Trial: RCT ; intravenous (IV) : antibiotics: ABX				

Overdiagnosis: Attribution of Symptoms to LB

Overdiagnosis has been described in cohort studies and case reports. The results are summarized in Table 1.

Cohort Studies

In France, two observational studies were conducted by Haddad et al. and published in 2019 [11, 12]. Rechallenging the PTLDS led to an overdiagnosis rate of 80.7%. In the second study, the overdiagnosis rate ranged from 85 to 90.4%. The differential diagnoses made were mostly psychiatric, rheumatological and neurological disorders. The categorization of differential diagnoses could be difficult, particularly for

disorders with somatic symptoms (e.g. fibromyalgia), which could be classified as psychiatric, rheumatologic, or no diagnosis [12]. Another observational study published in 2020 by Itani et al. included 15 patients with PTLDS for at least six months. The overdiagnosis rate was 100% [13].

In the United States, an observational study conducted by Kobayashi et al. was published in 2019. The overdiagnosis rate was 84.1% [22].

In Italy, Peri et al. analyzed medical records of 7 children with PTLDS. PTLDS had strongly influenced their schooling. A review of the clinical history revealed a 100% overdiagnosis rate [24].

Case Report

In 2015 Nelson et al. reported three cases in the United States of oncologic diagnostic errors and delays due to a diagnosis of PTLDS [25]. The first case was a 30-year-old man who had been suffering with joint pain and memory loss for 12 years. Following the onset of visual field deficit and syncopal episodes, he was diagnosed with a pituitary tumor. Facial morphological sequelae and cardiomyopathy appeared to be attributable to this diagnostic delay. The second case was a 30-year-old man with fatigue, loose stools and abdominal pain for 4 years. The diagnosis of PTLDS was made despite the absence of clinical signs of LB and living in an endemic area. The patient had received several cycles of oral and intravenous antibiotic therapy. Following discontinuation of his treatments, a gastric biopsy of a mesenteric lymph node and a PET scan revealed stage IV Hodgkin's lymphoma. The patient died 2 years later. The third case was a 50-year-old man with asthenia for 2 weeks and an influenza-like illness for 3 days. Doxycycline adapted to early LB was prescribed. Subsequently, an erythematous rash appeared under his left shoulder. Two more courses of doxycycline were performed with partial improvement. A diagnosis of PTLDS was made. Five months after this diagnosis, an infectious disease specialist requested a chest CT since the patient had smoked for 18 years. It confirmed the diagnosis of lung cancer.

In 2016, Di Battista described the case of a 61-year-old Italian woman with cognitive impairment [26]. Four years earlier, a diagnosis of LB had been made on the basis of a typical erythema migrans. In view of cognitive disorders and a major depressive syndrome persisting despite two courses of doxycycline, PTLDS was diagnosed. A PET scan and a brain MRI were performed after one year, due to the loss of autonomy and worsening of the disorders leading to the diagnosis of frontotemporal dementia.

Adverse effects of the drugs used

Adverse events were described in one randomized clinical trial (RCT), observational studies and case reports.

RCT and observational studies

In 2003, Krupp et al. conducted a randomized clinical trial with the aim of determining whether the symptoms of PTLDS regressed under antibiotic therapy [16]. The 55 patients included were randomized to receive 28 days of parenteral ceftriaxone or placebo. Diarrhea, the primary adverse event, was more common in the ceftriaxone group than placebo. Four serious adverse events required hospitalization.

In the French observational study by Itani et al. the 15 patients had received an average of 6.8 antibiotics for 476 days [13]. Adverse events were reported in 4 patients.

In France, in 2020, Trautmman et al. analyzed the results of a survey sent to 3 French associations of patients with PTLDS who had taken Disulfiram [21]. Of the 16 patients who responded, 13 had experienced various and moderate side effects (headache, dizziness, difficulty concentrating, etc.).

In the United States, in 2018, Goodlet et al. analyzed adverse reactions to oral or IV therapy in patients with PTLDS for more than 6 months [23]. The incidence rates of adverse events was higher in the IV therapy group and there were more hospitalizations.

Case Reports

In Australia, in 2018 Johnstone et al. reported the case of a 41-year-old female patient who was treated with weekly glutathione infusions and phosphatidylcholine in a clinic for PTLDS [27]. The patient consulted the emergency department for bacterial sepsis.

In 2016, Issacs reported the case of a 15-year-old girl diagnosed by a general practitioner specializing in LB on the basis of serology performed in a private laboratory [28]. She suffered from chronic fatigue and was treated with 2 weeks of induced hyperthermia and intravenous antibiotics. These therapeutics induced severe dehydration due to *Clostridium Difficile* colitis.

In the United States, in 2019, Shelton et al. reported the case of a 32-year-old woman presenting to the emergency department with fever, confusion, and dyspnea [29]. For the past two years and a diagnosis of PTLDS, she had been treated with multiple oral anti-infectives. The emergency department diagnosed multifocal pneumonia following infection of her central venous catheter with *Mycoplasma goodi*. Catheter removal and parenteral and then oral antibiotic therapy resulted in clinical improvement.

In 2016, Marks et al. reported the case of a 45-year-old woman presenting to the emergency department with a pruritic, diffuse rash with nausea and fever [30]. Six months prior to her emergency visit she had been diagnosed with PTLDS with babesiosis. She had received multiple antibiotics over the past 3 months. Emergency department blood tests showed neither active Lyme disease nor babesiosis, but a DRESS syndrome. Her condition improved with corticosteroids.

In Belgium, in 2016, De Wilde et al. reported the case of a 76-year-old woman who consulted the emergency department for malaise, vomiting, anorexia and dyspnea [31]. In 2007, she had experienced facial paresis four weeks after the onset of erythema. In 2009, a private clinic diagnosed PTLDS. She was treated for 20 consecutive weeks with 4 g of ceftriaxone IV per day. A few years later, faced with a recurrence of symptoms, the doctors proposed eight weeks of treatment. Three weeks after the start of this treatment, the emergency department diagnosed ceftriaxone-induced immunohemolytic anemia. Discontinuation of the antibiotic resulted in improvement.

Discussions

This review urges physicians to be cautious about the diagnosis of PTLDS because of the very frequent overdiagnosis. False positive tests and non-recognized tests performed in private laboratories contribute to overdiagnosis [7, 32]. These arguments explain why the ACR recommends not to test for Lyme disease as a cause of musculoskeletal symptoms without an exposure history and appropriate exam findings [14].

The most common adverse events were diarrhea, sometimes with *Clostridium difficile* colitis, electrolyte abnormalities, sepsis, bacterial and fungal infections, and anaphylactic reactions. These adverse effects were more frequent when the anti-infectives were administered by the IV route [13, 16, 23].

Strengths And Limitations

To our knowledge, this literature review is the first to compile errors, diagnostic delays and adverse events associated with the diagnosis and treatments of PTLDS. General underreporting of adverse events by caregivers and patients is a limitation to risk description [33]. Publication bias also limits the completeness of this work. This work may allow physicians managing patients with PTLDS to report past adverse events and publish diagnostic errors and delays due to attribution of symptoms to LB.

Conclusion

This review informs patients and physicians of the risks of PTLDS diagnosis and prolonged anti-infective treatment. The risks of these treatments described in this review highlight the importance of the ethical principle of non-maleficence, *primum non nocere*. It does not seem ethical to offer a patient a treatment that has unproven efficacy and documented risks.

Declarations

Ethics approval and consent to participate: not applicable

Consent for publication: non applicable

Availability of data and materials: All data generated or analysed during this study are included in this published article [and its supplementary information files].

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Authors Contribution:

Xavier Gocko had the idea of the subject

Sébastien Prat, Jacques Dalbin, Catherine Plotton et Xavier Gocko made acquisition, analysis, and interpretation of data and approved final version

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Figures

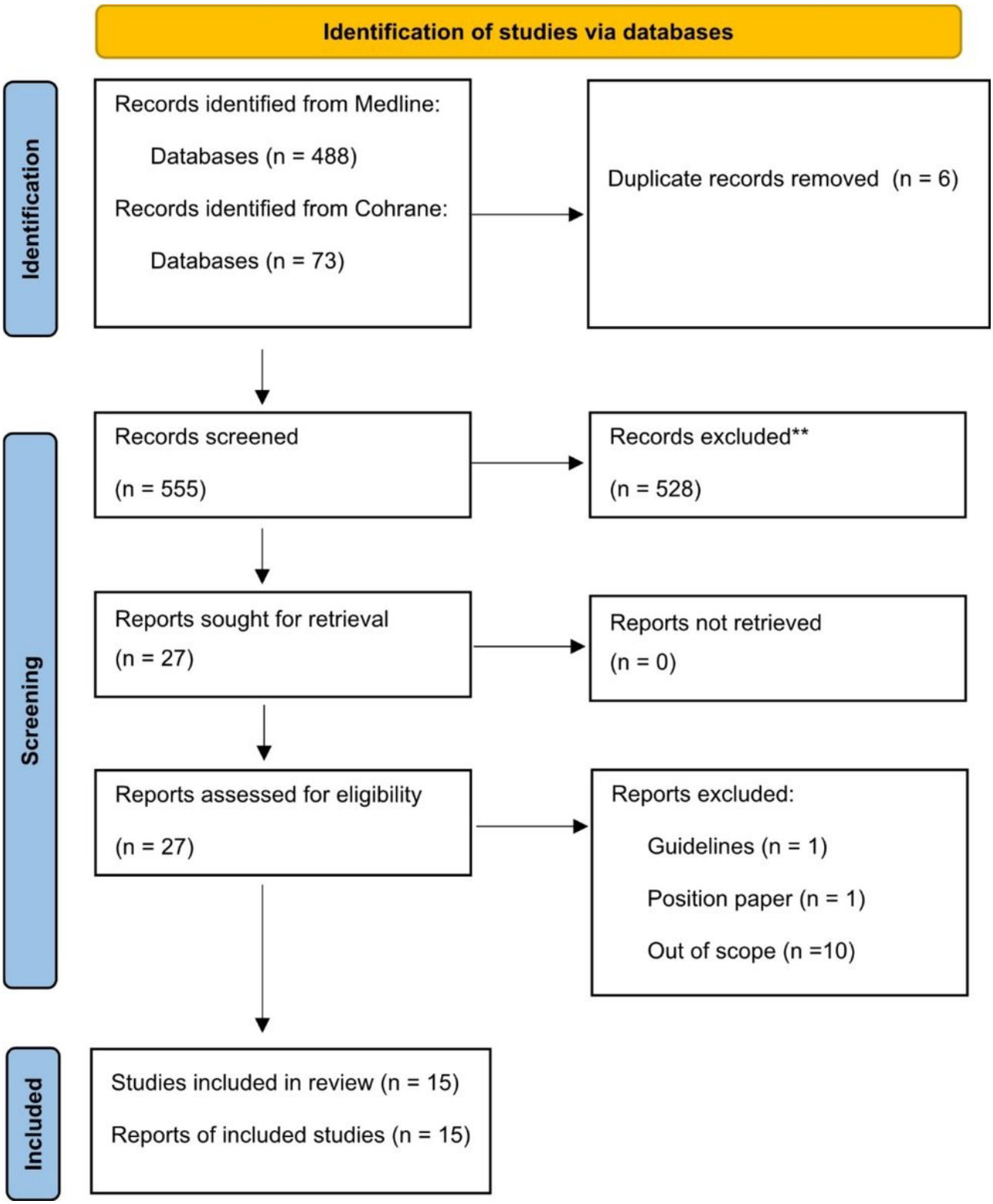

Figure 1

Flow diagram

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