Am. J. Trop. Med. Hyg., 96(1), 2017, pp. 46–52
doi:10.4269/ajtmh.16-0434

Review Article

The Jarisch–Herxheimer Reaction After Antibiotic Treatment of Spirochetal Infections: A Review of Recent Cases and Our Understanding of Pathogenesis

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Abstract. Within 24 hours after antibiotic treatment of the spirochetal infections syphilis, Lyme disease, leptospirosis, and relapsing fever (RF), patients experience shaking chills, a rise in temperature, and intensification of skin rashes known as the Jarisch–Herxheimer reaction (JHR) with symptoms resolving a few hours later. Case reports indicate that the JHR can also include uterine contractions in pregnancy, worsening liver and renal function, acute respiratory distress syndrome, myocardial injury, hypotension, meningitis, alterations in consciousness, seizures, and strokes. Experimental evidence indicates it is caused by nonendotoxin pyrogen and spirochetal lipoproteins. Mediation of the JHR in RF by the pro-inflammatory cytokines tumor necrosis factor (TNF), interleukin (IL)-6, and IL-8 has been proposed, consistent with measurements in patients' blood and inhibition by anti-TNF antibodies. Accelerated phagocytosis of spirochetes by polymorphonuclear (PMN) leukocytes before rise in cytokines is responsible for removal of organisms from the blood, suggesting an early inflammatory signal from PMNs. Rarely fatal, except in neonates and in pregnancy for African women whose babies showed high perinatal mortality because of low birth weight, the JHR can be regarded as an adverse effect of antibiotics, necessary for achieving a cure of spirochetal infections.

INTRODUCTION

The Jarisch–Herxheimer reaction (JHR) was named after European dermatologists who described in 1895 and 1902 patients with syphilis who developed exacerbations of their skin lesions after treatment with mercurial compounds.[1–3] After penicillin became the drug of choice for syphilis in the 1940s, the JHR occurred during the first 24 hours of treatment in primary and secondary disease as well in general paresis of the insane manifesting as fever, chills, headache, myalgias, and intensification of skin rashes.

In other spirochetal infections, including Lyme disease (LD), leptospirosis, and relapsing fever (RF), a similar reaction was reported after treatments with penicillins, tetracyclines, and erythromycin. In addition, newer antimicrobials such as cephalosporins, meropenem, ciprofloxacin, levofloxacin, clarithromycin, and azithromycin can provoke the JHR.[4–10] The purpose of this review is to update reports of the JHR in the past 25 years and to examine our understanding of its pathogenesis. Case reports were included if listed in PubMed during 1990–2015 under JHR, *Treponema*, *Leptospira*, or *Borrelia*. Studies of pathogenesis included older publications assembled by cross-referencing of papers about mechanisms of the JHR.

FREQUENCY AND SEVERITY OF THE JHR

Syphilis. Syphilis persists as the leading spirochetal infection that gives rise to a JHR. The common signs of JHR were fever and exacerbation of skin rashes. Frequency of JHR occurrences in syphilis and other spirochetal infections shown in Table 1 varied from 1 to 100% in observations about antimicrobial therapy,[11–33] indicating large variations in patients' susceptibilities as well as varying criteria used by observers of the reaction.

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In a prospective study of 33 pregnant women in Texas with syphilis, who were treated with benzathine penicillin, 15 (45%) developed a JHR that was more common in primary and secondary infections than in latent infections; it started 2–8 hours after therapy, peaked at 6–12 hours, and resulted in fever and uterine contractions in most women, resulting in delivery of three infants with congenital syphilis.[13] In 13 pregnant women in Chicago with syphilis who developed a JHR, uterine contractions were noted that resolved within 24 hours.[14] A woman in Texas with preterm labor given penicillin for prophylaxis of *Streptococcus agalactiae* vaginal carriage developed chills and tachycardia, only to be found seropositive for syphilis with papulosquamous skin lesions after delivery of her baby with congenital infection.[34] A woman in Japan presented in labor, received ampicillin prophylaxis for *S. agalactiae* and delivered 6 hours later a baby with a diffuse skin rash including blisters that suggested a JHR along with signs of congenital syphilis; after delivery, the baby received ampicillin, followed an hour later by fever and tachypnea, suggesting another JHR.[35]

Case reports revealed the JHR in syphilis to be multifaceted in organs affected. A characteristic patient in New York, a 45-year-old human immunodeficiency virus (HIV)–positive man with rash, was treated with penicillin intravenously. An hour later, he developed a chill with a pulse rate of 140 and respirations of 28 per minute. This JHR was initially attributed to penicillin allergy.[36] In a 45-year-old man in Ottawa with secondary syphilis as well as coinfection with HIV and hepatitis C virus, penicillin caused a JHR along with worsening liver function.[37] From six case reports of neurosyphilis, additional neurological dysfunctions during the JHR occurred.[15,38–42] Hallucinations or changes in consciousness or orientation were noted in three cases, seizures in three, abnormal magnetic resonance imaging or electroencephalograph in three, hemiparesis in two, and one each of facial nerve weakness and diplopia. In a Japanese man with dementia, treatment of neurosyphilis with penicillin provoked a JHR, from which he recovered, but his dementia persisted.[43]

Lyme disease. In trials shown in Table 1, the range of JHR frequency was 7–30%, indicating a trend toward lower

TABLE 1
Frequency of JHR in spirochetal infections in prospective studies, randomized trials of antimicrobial drugs, surveys, and meta-analyses

Clinical condition	Frequency as percent of treated patients who developed a JHR	Reference
Syphilis		
Primary, secondary, and early latent treated with penicillin		
RPR titer ≥ 1:32	41	11
RPR titer < 1:32	16	11
HIV positive	35	11
HIV negative	25	11
Penicillin	56	10
Azithromycin	14	10
Secondary syphilis treated with penicillin	9	12
Syphilis in pregnancy	40–45	13,14
Neurosyphilis	8–75	15–17
Lyme disease, early with erythema migrans		
Azithromycin	7	18
Amoxicillin	15	18
Amoxicillin	8	19
Cefuroxime axetil	8	19
Amoxicillin	10	9
Clarithromycin	11	9
Cefuroxime axetil	12	20
Doxycycline	12	20
Cefuroxime axetil	29	21
Doxycycline	8	21
Erythromycin, penicillin, tetracycline	14 overall, more with penicillin and tetracycline than with erythromycin	22
Azithromycin	13	23
Doxycycline	12	23
Azithromycin	5	24
Doxycycline	10	24
Azithromycin	30	25
Doxycycline	30	25
Penicillin	19	25
Leptospirosis		
Meta-analysis of 976 cases in trials	9, mostly treated with penicillin or ampicillin	26
Family of four persons	50, those treated with ceftriaxone or meropenem and doxycycline	6
Penicillin	83	27
Relapsing fever		
Tick-borne		
Surveys of cases in United States and Canada	39	28
Surveys in Iran	1	29
Louse-borne		
Meta-analysis of 438 patients in six randomized trials		
Penicillin	37	30
Tetracycline	48	30
Erythromycin	80	31
Penicillin	67	31
Tetracycline	96	31
Slow-release penicillin*	100	32
Tetracycline*	100	32
Tetracycline	47	33
Procaine penicillin 400,000 units	31	33
Procaine penicillin 200,000 units	28	33
Procaine penicillin 100,000 units	5	33

HIV = human immunodeficiency virus; JHR = Jarisch–Herxheimer reaction; RPR = rapid plasma reagin.
*Frank rigors in only 1/6 patients treated with penicillin, but all patients treated with tetracycline had rigors.

frequency than for syphilis. Furthermore, the reactions in LD were clinically milder than in the other diseases, without organ dysfunction or need for hospitalization. A severe case was a 31-year-old woman in Connecticut with a tick bite followed by erythema migrans, who received amoxicillin, which an hour later provoked chills, a temperature of 40°C, and hypotension that resolved over 3 hours while getting 3 L of intravenous saline.[44]

Leptospirosis. A review of 976 cases of leptospirosis treated with antibiotics revealed detection of JHR in 92 patients, for an incidence of 9%.[26] Only one of the patients died. He was a 20-year-old man in Ireland with jaundice and renal failure, who deteriorated after receiving penicillin, expiring the next day.[45] Most of the cases of JHR were from one study in Malaya in 1957 that reported a JHR in 70 of 84 (83%) patients who received intramuscular penicillin injections.[27]

A 29-year-old woman in France, who acquired leptospirosis 10 days after falling into a river while canoeing, experienced a JHR 4 hours after receiving amoxicillin when nuchal rigidity also developed; her spinal fluid showed elevated polymorphonuclear (PMN) cells and high protein concentration.[46] A 59-year-old man in Japan, 2 weeks after drinking swamp water in Okinawa, presented with fever and jaundice leading to a diagnosis of leptospirosis; 2 hours

after treatment with ceftriaxone, he became more febrile with shock requiring vasopressors and intubation before recovering.[4] Two hours after treatment with ceftriaxone for leptospirosis, a 49-year-old man in United Kingdom manifested a JHR with rising temperature, tachycardia, and elevation of creatinine necessitating intensive care unit (ICU) monitoring and hemodialysis before recovering.[5] A 42-year-old man in Japan with leptospirosis treated with ceftriaxone developed on the next day multi-organ failure, hemoptysis, and radiographic signs of pulmonary alveolar hemorrhage with recovery 6 days later.[47] Two of four family members in Switzerland after a white-water rafting trip to Thailand acquired leptospirosis and developed a JHR after treatment with ceftriaxone, meropenem, and doxycycline with serious consequences of hypotension, requiring adrenergic therapy in one case, as well as impaired liver and renal function.[6] A 60-year-old farmer in Australia with fever, confusion, and thrombocytopenia developed a JHR 2 hours after receiving penicillin and ceftriaxone followed by uncomplicated recovery.[48] A 51-year-old man in United Kingdom with fever, jaundice, and renal failure developed a JHR 5 hours after penicillin therapy and required hemodialysis before recovering.[49] A 21-year-old man in United Kingdom after falling into a river from his canoe became febrile with vomiting and diarrhea; a JHR occurred 4 hours after penicillin treatment followed by an uneventful recovery.[49]

Relapsing fever. In RF, the frequency, severity, and timing of the JHR are more predictable than in other infections. RF differs from other infections by having large numbers of organisms visible in blood plasma, convenient for rapid diagnosis in blood smears as well as following clearance of spirochetes after treatment. During the JHR, which occurs in most patients 1–2 hours after antibiotic treatment, spirochetes disappear from the blood within about 5 hours. Except in Ethiopia, where louse-borne relapsing fever (LBRF) is prevalent, all cases reported in recent years from other African countries, North America, the Middle East, and Spain are tick-borne relapsing fever (TBRF).[28,29,50] An exception was two young male migrants from Eritrea in Netherlands in 2015, who had traveled through Ethiopia, had LBRF, and developed severe JHRs 2 hours after treatment, and recovered after care in the ICU.[51] In the United States and Canada between 1977 and 2000, 450 patients with TBRF were recorded.[28] Only one death occurred, in a neonate, whose mother was also infected. In 129 patients with clinical information about treatment available, 50 of them (39%) showed a JHR (Table 1). Most had reactions within 2 hours after treatment, consisting usually of chills, sweating, tachycardia, and hypotension without cutaneous manifestations. In one patient, the JHR started 30 minutes after an intravenous dose of doxycycline. In a meta-analysis of six studies in Ethiopia of patients with RF, a JHR occurred in 89 of 239 patients (37%) treated with penicillin and in 96 of 199 patients (48%) treated with tetracycline.[30] Only four deaths were reported in each group for a case-fatality rate of 8/438, or 2%. A 59-year-old woman in the United States on steroids for thrombocytopenia with a heavy infection was treated with doxycycline and ceftriaxone.[52] She did not show a JHR initially, perhaps because of steroid treatment before antibiotics, but was hospitalized 3 days later with acute respiratory distress syndrome and pulmonary edema, requiring mechanical ventilation with eventual recovery. A 75-year-old woman in United States developed a JHR 4 hours after receiving levofloxacin that was followed by chest pain and low back pain as well as a rise in troponin I before recovering.[8] Two hours after intravenous doxycycline for TBRF, a 12-year-old girl in Spain developed vomiting, diminished consciousness, a blood pressure of 60/30 mmHg, and cardiac dysfunction shown by decreased ventricular ejection fraction and a rise in blood level of troponin I requiring mechanical ventilation and positive end-expiratory pressure for recovery.[50] After returning from travel in Senegal, a 47-year-old Belgian woman developed RF and experienced a JHR after treatment with doxycycline.[53]

Among 137 pregnant women in Tanzania with treated RF, 80 went into labor with the sad result that 38 infants died (47.5%), mostly because of low birthweight; however, only 1.5% of the women were noted to have a JHR and 1.5% of the women died. In these 80 women, it was unclear whether their premature labor was caused by their RF infections mainly or by the antibiotic treatment.[54] A 19-year-old woman in Tanzania with RF delivered her baby, after which she was treated with penicillin, only to die the same day during a JHR.[55] Neonatal infections, likely acquired from maternal infections during birth or across the placenta before birth, are rare but often fatal. In a report of five cases of neonatal RF in Tanzania, three died within a few hours after penicillin treatment.[56] Heavy spirochetemia was blamed for their deaths, but JHR cannot be excluded in case reports without information about changes in vital signs after treatment.

PATHOGENESIS OF JHR

Inflammatory substances in spirochetes. Clinical observations of patients with the JHR suggested a role for endotoxin,[57–59] but experimental studies showed that spirochetes do not have biologically active endotoxin as defined by the limulus test.[60–63] Substances other than endotoxin as well as mechanisms were described.[64–71] In *Treponema pallidum*, lipoproteins were identified as likely responsible for inflammatory signs because they stimulate macrophages to produce tumor necrosis factor (TNF).[64] In *Borrelia Burgdorferi*, the outer surface protein A lipoprotein stimulates cells in culture to produce transcription factors for cytokines.[65] *Borrelia recurrentis* from human plasma was also negative for endotoxin by the limulus test but was pyrogenic in rabbits.[66] The nonendotoxin pyrogen could be the same as the lipoprotein. Lipoprotein of the outer membrane proteins of leptospires caused inflammation in mouse kidney cells.[67]

Cytokines. In patients with RF, plasma concentrations of the cytokines TNF, interleukin IL-6, and IL-8 were measured as sharply increasing at 2–4 hours after penicillin treatment when patients were experiencing a JHR, with a return toward baseline levels 12 hours after therapy (Figure 1).[68] Anti-TNF antibodies administered before antibiotic treatment prevented or attenuated the JHR, while also reducing levels of IL-6 and IL-8 during the reactions.[72,73] The cytokine response to *Borrelia* spirochetes requires recognition by Toll-like receptor 2 (TLR2) or TLR1/TLR2 heterodimers on the surfaces of phagocytes.[74,75] The anti-inflammatory cytokine IL-10 was very elevated in LBRF patients, but treatment of patients with recombinant IL-10 did not prevent JHR and did not inhibit rises of TNF, IL-6, or IL-8 during the JHR.[76]

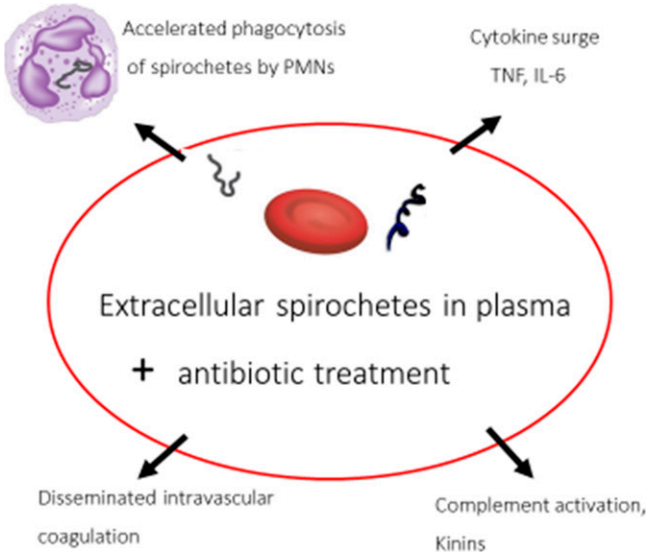

FIGURE 1. Proposed pathogenesis of Jarisch–Herxheimer reaction in relapsing fever. PMNs = polymorphonuclear leukocytes; TNF = tumor necrosis factor; IL-6 = interleukin-6.

Phagocytosis. At the onset of the JHR of LBRF, about 2 hours after antibiotic treatment, phagocytosis of spirochetes by blood PMNs had increased from a mean of 5% of cells that contained spirochetes before treatment to 23%, and addition of antibiotic to blood obtained before treatment caused a sharp rise in numbers of PMNs containing spirochetes during 0.5–2 hours of incubation.[69] Spirochetes were demonstrated in PMNs with the Dieterle silver stain and in phagocytic vacuoles by electron microscopy.

In vitro studies of phagocytosis by monocytes showed that live, whole *B. burgdorferi* spirochetes stimulated ingesting monocytes to produce cytokines better than heat-killed or lysates of organisms.[77] Apoptosis or programmed cell death of monocytes after phagocytosis of *Borrelia* could also be a factor driving the JHR.[77] After phagocytosis, *B. burgdorferi* uses TLR2 signaling to give a pro-inflammatory cytokine response via the adapter molecule MyD88.[78–80]

Disseminated intravascular coagulation. Biopsy of the petechiae was performed in patients with RF and resulted in thrombocytopenia due to disseminated intravascular coagulation (DIC) but not vasculitis or endothelial damage.[66] Conjunctival hemorrhages in a patient in Spain was also associated with thrombocytopenia.[81]

Complement activation, kinins, and histamine. Serum levels of hemolytic complement and properdin were reduced in patients with RF before and after antibiotic treatment, suggesting consumption of complement in the alternative complement pathway due to phagocytosis of *Borrelia*.[70] Other studies of RF, however, indicated that complement was not activated.[32] Elevated blood levels of histamine and kinins were measured in patients with syphilis and RF before and after the JHR, suggesting roles for these mediators of inflammation.[70,71]

DISCUSSION

The JHR often goes unrecognized and is underreported. Its symptoms of chills, fever, myalgia, and skin rash are often present before antibiotic treatment, so the worsening of these symptoms after antibiotic treatment can be overlooked as signs of the underlying infection. Another reason for underdiagnosis is confusing the JHR with antibiotic allergy. Physicians need to anticipate a JHR when treating spirochetal diseases to provide supportive care of monitoring vital signs and administering fluids. Clinical acumen to detect a JHR when using antibiotics for other purposes than treating spirochetal infections, like prophylaxis of *S. agalactiae* during pregnancy, can uncover a diagnosis of syphilis.[34]

Warnings about severe reactions or fatal outcomes are exaggerated and inappropriate in most situations because fatalities are rare.[26,30,82] No deaths due to JHR in syphilis or LD were evident in this review. The small number of fatalities during the JHR could suggest that these patients were so severely affected by their leptospirosis or RF before treatment that they would have died without antibiotic treatment. Clinical descriptions of the JHR indicate that its definition should be broadened from chills, rising temperature, and intensification of skin rash to include sometimes meningitis, pulmonary failure, liver and renal dysfunction, myocardial injury, premature uterine contractions in pregnant patients, and worsening cerebral function as well as strokes and seizures.

In pathogenesis, not all JHRs are alike. The timing of the reaction after treatment in syphilis is to start at 4 hours, peak at 8 hours, and subside by 16 hours,[1] whereas in RF it starts at 1–2 hours, peaks at 4 hours, and subsides by 8 hours. In addition, blood white cell counts in syphilis show leukocytosis and lymphopenia but show leukopenia with neutropenia in RF.[32,83] Intensification of skin rashes occurs in syphilis and LD but not in leptospirosis and RF because spirochetes in syphilis and LD are plentiful in skin but localized more to blood and other body fluids in leptospirosis and RF.[84]

The JHR has been variously attributed by authors for more than a century to release of toxins by dying spirochetes, hypersensitivity to spirochetes, removal of dead spirochetes by phagocytic cells, complement activation, DIC, and mediators of inflammation including cytokines and histamine. However, many of these mechanisms are unsupported and probably wrong. Spirochetes of LD need 48–72 hours of exposure to antibiotics before they die,[85] ruling out a rapid lethal antibiotic effect. Besides, destruction of spirochetes followed by release of toxins is not compatible with findings of intact spirochetes in phagocytic vacuoles hours after treatment.[69] Although hypersensitivity reactions have been proposed,[86] studies of leukocyte counts in patients as well as inconsistent results from injections of leukocytes and serum into skin of patients proved that allergic or other hypersensitivity reactions were unlikely.[83] The earliest event in the JHR demonstrated to date in the JHR of RF, which is a likely trigger, is the rapid uptake of antibiotic-altered spirochetes by blood PMNs, resulting in removal of spirochetes from the blood. Before the JHR, most spirochetes in the body are in extracellular spaces of the skin or in blood plasma,[84] where they usually elicit only mild or moderately severe inflammation. After antibiotic treatment, spirochetes are rendered more susceptible to PMN phagocytosis likely caused by an alteration of the microbial surface to expose antigens and molecular

patterns that allow antibody and complement to bind more effectively for phagocytic uptake. Once inside, PMN spirochetes probably provoke more severe inflammation. Studies of phagocytosis of spirochetes by mononuclear cells in vitro suggest roles for mononuclear phagocytes in pathogenesis of the JHR.[64,77]

Causes of inflammation in the JHR are multifactorial. Spirochetal inflammatory substances include lipoproteins and nonendotoxin pyrogens that cause rises in cytokines.[64–67] Studies in patients with RF indicate that in the first 2 hours after antibiotic treatment, when spirochetes are cleared from blood, rises in concentrations of pro-inflammatory cytokines occur.[68,82] It is unlikely, however, that rising blood levels of the cytokines TNF, IL-6, and IL-8 initiate the JHR because the chill and temperature rise start as early as 30 minutes to 1 hour after antibiotic treatment,[28,68,73] when blood levels of these cytokines, already elevated before antibiotic treatment, stay about the same for 30 minutes to 1 hour after treatment.[68,70,82] Rises of cytokines are evident only 2–4 hours after antibiotic when the JHR is already fully expressed. Thus, the rises of cytokines appear to be the result of the JHR rather than its cause, while contributing to the intensity of the reaction as shown by the amelioration by anti-TNF antibodies.[72]

With the discovery that plasma cytokines rise in the JHR, it was inevitable that an analogy was drawn between the JHR and septic shock caused by other bacteria. The systemic inflammatory response syndrome of sepsis is similar in both conditions. However, the JHR is short lived over several hours, after which patients are improved, rarely die, and cytokines return to pre-JHR levels.[68] Only two patients in this review, both with leptospirosis, required vasopressors for severe hypotension,[4,6] whereas in septic shock the inflammatory response is more sustained with high case-fatality rates despite the use of vasopressors. Sustained shock in sepsis can be correlated with endothelial cell damage leading to failure of the microcirculation, which does not occur in JHR.[66] Favorable prognosis in the JHR can be explained in part by spirochetes having a nonendotoxin pyrogen that is much less potent and less lethal than endotoxin.[66]

Efforts to prevent the JHR have been tried and are currently used by some physicians who give corticosteroids before penicillin in neurosyphilis or early syphilis to prevent or to blunt the severity of a JHR,[41,87–89] but it is not clear whether this therapy is effective enough to be indicated.[3] A possible disadvantage of corticosteroids would be inhibition of phagocytosis that is useful for clearing spirochetes during the JHR and for preventing relapses.[90] Use of acetaminophen or hydrocortisone 2 hours before and 2 hours after erythromycin for RF did not prevent the JHR but ameliorated it by lessening the reduction of systolic blood pressure.[31] The opioid antagonist meptazinol given with and 30 minutes after tetracycline to patients with RF in Ethiopia delayed the onset of the JHR and diminished its severity.[91] Side effects, including vomiting in half the patients, would limit the usefulness of this drug. Lower frequencies of JHR with azithromycin in syphilis and LD could favor use of macrolides,[10,18] but this trend was not consistent across all studies. Low doses and slow-release forms of antibiotics were tried,[32,33] but are not recommended because they allowed prolonged symptoms with potential for relapses. With the demonstration that anti-TNF antibody therapy could prevent and ameliorate the JHR in RF,[72] it was hopeful that an effective therapy could be applied to patient care. Another anti-cytokine drug, pentoxifylline, failed to prevent the JHR and cytokine rises in RF.[92] The prognosis is so favorable for full recovery in a few hours in most patients given supportive care and adequate fluids, however, that anti-cytokine treatment is probably not justified.

Received May 31, 2016. Accepted for publication September 20, 2016.

Published online October 24, 2016.

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