REVIEW ARTICLE

Treatments and new perspectives of Antiphospholipid Syndrome in pregnancy

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Abstract

Antiphospholipid syndrome (APS) is an autoimmune disease characterized by the remarkable presence of persistent antiphospholipid antibodies (aPL), thrombosis and/or recurrent miscarriage.. The presence of aPL antibodies is considered the major adverse prognostic factor in patient with Lupus. The pathogenesis of APS is still poorly understood, due the high complexity of events involving three major altered components: platelets, coagulation cascade, and endothelial cells. APS during pregnancy represents an increased risk of miscarriage and thrombotic events for the woman and fetus. The treatment of APS is based on lifetime anticoagulation therapy, using Aspirin which may be combined with heparin. The combination of low molecular weight heparin with low dose Aspirin leads to the highest success rates and thus its recommended for use throughout pregnancy until 6 weeks after child-birth. although there is still some controversy to the use of aspirin with LMWH/UFH, it should be considered as gold-standard for APS treatment for women during pregnancy and post-partum. New possibilities of treatment for pregnant woman with APS has emerged due to an increase in the number of medical reports and case studies, in addition to advances in the development of new drugs. In spite of these great attempts to develop new therapies, the treatment outcomes for APS in pregnancy remain poor. the development of new therapeutic modalities with other well-designed clinical trials are needed in order to treat and/or prevent thrombosis in pregnant patients with APS and increase the live birth rate.

Keywords: Antiphospholipid Syndrome; Pregnancy; Thrombosis and Miscarriage; Hydroxychloroquine; Aspirin; Heparin.

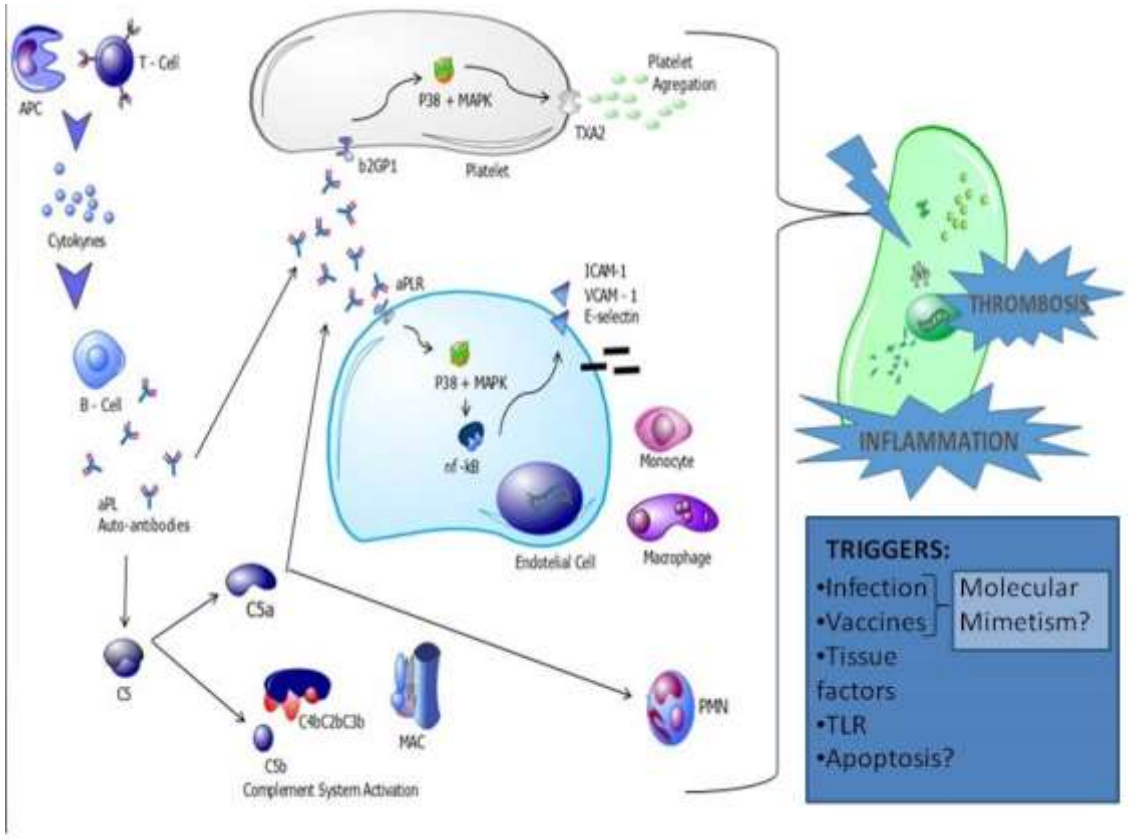
1. INTRODUCTION

Antiphospholipid Syndrome (APS) is an autoimmune syndrome characterized by production of antiphospholipid antibodies, recurrent miscarriage and/or thrombosis. [1–3]. In 1963, Bowie et al.[4], observed that some patients with Systemic Lupus Erythematosus (SLE) and Lupus Anticoagulant (LA) had thrombosis instead of bleeding, as might be expected when the coagulation test was prolonged [5]. In addition, some patients had false-positive results for the VDRL test (Venereal Disease Reference Laboratory). One of VDRL components is cardiolipin, a phospholipid from cardiac muscle composes the test reagent. In 1983 a test was developed to determine the anti-cardiolipin antibody levels (aCL) in plasma samples [6,7]. Currently, several antiphospholipid antibodies (aPL) have been identified as LA; aCL, anti-β2GPI (anti-beta 2 glycoprotein I), aPT (anti-prothrombin), aPS (anti-phosphatidylserine), and aPE (anti-phosphatidylethanolamine). In APS, LA, aCL and anti- β2GPI are often present. The presence of aPL antibodies is considered the major adverse prognostic factor in patient with Lupus.[3,6–14].

1.1. *Pathogenesis*

The pathogenesis of APS is still poorly understood due to the high complexity of events (figure 1) involving three major altered components: platelets, the coagulation cascade, and endothelial cells.[15] Although the pathogenesis of APS remains uncertain, the interaction of aPL with anionic phospholipids and β2GP1 is associated with the beginning of an abnormal coagulation cascade and thrombus formation[16,17]. However, the mechanisms that generates these antibodies (aPL) is unknown and needs further investigation.

Figure 1. Schematic mechanism of Antiphospholipid Syndrome.



Endothelial cells have several proteins in their phospholipid membrane: annexin A5 (AnxA5), β2GPI, E-selectin, ICAM-1, and VCAM-1[18]. AnxA5 are strong anticoagulant proteins that inhibit the binding of coagulation factors to endothelial cells[19]. aPL can interrupt AnxA5 function leading to a coagulative state [20]. β2GPI is a protein cofactor which aids the anchoring of the phospholipid to the cell membrane, and can be disrupted by aPL which has anti-β2GPI activity [8]. Although the physiological role of β2GPI is unclear, the molecule appears to inhibit thrombosis through the extrinsic pathway coagulation cascade, by reducing the conversion of prothrombin to thrombin, and by also inhibiting the cascade activation through the blocking of intrinsic coagulation factors[11,14,21,22].

Moreover, aPL boosts/ upregulate the expression of adhesion molecules (E-selectin, ICAM-1, and VCAM-1)[23], the secretion of proinflammatory cytokines (IL-1b and IL-6), and the production of platelet TXA2, a potent platelet aggregating agent and vasoconstrictor, leading to a high thrombogenic state[8,15]. In addition, *in vivo* studies show that aPL activation of the complement system, especially the C5a component, generates a hypercoagulable state and subsequent fetal loss[24].

1.2. *Diagnosis*

APS is characterized by clinical and laboratory manifestations that appear when the immune system recognizes the phospholipids from the cell membrane as a non-self-antigen, thus producing autoantibodies[21,25]. A patient is diagnosed with APS when, at least, one clinical and one laboratory parameters are positive [26]. The clinical and laboratory criteria are shown in Table 1, which has been termed the Updated Sapporo Classification[27]. These clinical criteria include the vascular thrombosis, characterized by one or more episodes in any tissue or organ and the morbidity during pregnancy, in the case of three or more consecutive miscarriages less than 10 weeks apart. The laboratory criteria include immunoassay (such as ELISA) to identify aCL and anti-β2GPI antibodies, and coagulation tests for LA. These criteria require positivity that occurs on two or more occasions over a 12 weeks interval[11,14,17,22,25,28–30]. However, some authors have cautioned the use of this classification criteria due the heterogeneity of aPL[31].

Table 1. Updated Sapporo APS Classification Criteria[26,31]

Clinical criteria
1. Vascular thrombosis. a) One or more clinical episodes of arterial, venous, or small vessel thrombosis in any tissue or organ. 2. Pregnancy morbidity a) One or more unexplained deaths of a morphologically normal fetus at or beyond the 10th week of gestation; or b) One or more premature births of a morphologically normal neonate before the 34th week of gestation because of eclampsia, severe preeclampsia, or recognized features of placental insufficiency; or c) Three or more unexplained consecutive spontaneous abortions before the 10th week of gestation, with maternal anatomic or hormonal abnormalities and paternal and maternal chromosomal causes excluded.
Laboratory criteria
1. Lupus anticoagulant present in plasma on two or more occasions at least 12 weeks apart, detected according to the guidelines of the International Society on Thrombosis and Hemostasis; 2. Anticardiolipin antibody of immunoglobulin (Ig)G or IgM isotype in serum or plasma, present in medium or high titer (>40 GPL or MPL, or >99th percentile), on two or more occasions at least 12 weeks apart, measured by a standardized ELISA; 3. Anti-b2-glycoprotein I antibody of IgG or IgM isotype in serum or plasma (in titer >99th percentile) present on two or more occasions at least 12 weeks apart, measured by a standardized ELISA.
APS presence confirmed if at least one of the clinical criteria and one of the laboratory criteria are met

1.3. *Epidemiology*

Interestingly, approximately 40% of patients with SLE have aPL (one-third are aCL positive, and 15% LA positive) and 30 to 40% of this group will develop APS[28,32]. Despite the prevalence of aPL in 1 to 5% of the population, the prevalence of APS does not seem to exceed 1% at age of 31 [17,30,33]. A study by Euro-Phospholipid Project examined 1000 patients diagnosed with APS and found a 5:1 ratio of women and men, respectively. Furthermore, 98.5% of the cases were Caucasian[12]. A study with 109 pregnant women diagnosed with intrauterine fetal death at approximately 20 weeks gestation, showed that 33.3% of the deaths were of unknown origin. In addition, 18.3% of these pregnant women had antibodies which were associated with aCL[34].

1.4. *Antiphospholipid Syndrome in Pregnancy*

APS in pregnancy represents an increased risk for miscarriage and thrombotic events for the woman and fetus[35]. In fact, if a thrombotic event has occurred in the previous six months or if a woman presents with either uncontrolled hypertension or pulmonary hypertension (high risk of maternal death), pregnancy should be avoided[2,8]. The severity of complications and maternal-fetal consequences vary according to the aPL type, since it can: inhibit the secretion of chorionic gonadotropin, interfere with the placental anticoagulant protein (PAP), increase thromboxane synthesis and decrease the prostacyclin production. The presence of these antibodies is associated with morbidity and mortality, such as recurrent fetal loss (about 10 to 15% of cases are attributed to APS), repeated miscarriage (about 10% of women have APS), preterm labor, premature rupture of membranes, intrauterine growth restriction, stillbirth, hypertension in pregnancy, placental insufficiency, and preeclampsia [7,10,21,25,36]. However, with proper clinical monitoring, the live birth rate is about 80%[2,8].

Pregnancies with APS are a challenge for clinicians because of complications potential both for mother and fetus. In addition, recurrent miscarriage can affects mother social and psychologically. In this review, we discuss the current recommendations for the clinical treatment of APS in pregnancy as well as its limitations.

2.0. TREATMENTS APS IN PREGNANCY

Drug therapy for APS has been evaluated in several studies[7,11,14,37,38]. These treatments included daily low dose Aspirin, Aspirin with prednisone, Aspirin and unfractionated heparin, Aspirin and low molecular weight heparin, intravenous immunoglobulins, steroids, and plasma exchanges. All these treatments showed improvement in live birth rates; however, there are some associations with an increased number of adverse reactions. The combination of low molecular weight heparin with low dose Aspirin leads to the highest success rates and thus its recommended for use throughout pregnancy until 6 weeks after child-birth.

Warfarin is contraindicated in early pregnancy because it can lead to teratogenicity, especially in the first trimester. Women on anticoagulation therapy with Warfarin that become pregnant should stop its use and replace the Warfarin during the first 6 weeks of gestation[30].

2.1. Corticosteroids

Corticosteroids, specifically prednisone, have failed to prevent fetal death[39], and also leads to an increased number of adverse reactions such as preterm births, diabetes, and hypertension[2,7,40,41]. Cowchock and colleagues (1992)[42] managed a multicenter randomized trial and showed that low-dose heparin should be used instead of prednisone. Similarly,

Silver and colleagues (1993)[43] conducted a cohort study to compare the use of prednisone with low dose of Aspirin as compared to Aspirin alone. At the end of study the authors concluded that the use of prednisone did not improve the outcome and increased morbidity due the complications, such as maternal hypertension and gestational diabetes [44].

2.2. Immunoglobulins

Intravenous immunoglobulin (IVIG) showed a significant difference from others therapeutic treatments, once IVIG reduced the circulating aPL, specially aCL and LAC[45,46]. IVIG is commonly used when conventional treatments fail since they have low adverse effects and are acceptable for administration during pregnancy[47]. However, Santamaria *et al* (2005) have shown that treatment with IVIG in women with APS did not improve neonatal outcomes when compared to treatment with heparin/Aspirin[7]. The treatment with IVIG produced a slight reduction in cases of fetal growth restriction (0% versus 33% for the placebo group) and neonatal intensive care unit admissions (20% versus 44%, placebo group)[48]. Moreover, there was a 90% gestational success rate in the group treated with heparin, aspirin and IVIG [49]. These results show the effectiveness of treatment with IVIG although its mechanisms are yet to be unveiled and more, the use is restricted by its cost[47].

2.3. Aspirin and Heparin

Aspirin and heparin are widely recommended as the treatment for APS in pregnancy (see table 2) [8,10,44]. Aspirin can reduce the production of thromboxane A_2 (TXA_2) and the formation of prostaglandin I_2 (PGI_2), two molecules related to pregnancy hypertension and pre-eclampsia. Furthermore, low-dose Aspirin (LDA) is a potent stimulator of interleukin-3 (IL-3), which is required for trophoblast invasion and placenta formation [11,14,50,51].

Table 2. Suggested schedules for the treatment of APS in pregnancy with aspirin and/or subcutaneous heparin

APS without previous thrombosis and recurrent early miscarriage	LDA (75–100 mg/day) alone or in combination with heparin: UFH (5.000-7.500 U/12h in the first quarter; 5.000-10.000 U/12h in the second and third trimesters); LMWH: 1) enoxaparin 40 mg/day, or dalteparin 5.000 U/day 2) enoxaparin 30 mg /12h, or dalteparin 5.000 U/12h
APS without previous thrombosis and fetal death (more than 10 weeks' gestation) or pre-eclampsia or severe placental insufficiency	LDA (75–100 mg/day) alone or in combination with heparin: UFH (7.500-10.000 U/12h in the first quarter; 10.000 U/12h in the second and third trimesters); LMWH: 1) enoxaparin 40 mg/day, or dalteparin 5.000 U/day 2) enoxaparin 30 mg /12h, or dalteparin 5.000 U/12h
Antiphospholipid syndrome with thrombosis	LDA (75–100 mg/day) alone or in combination with heparin: UFH (7.500 U/8-12h); LMWH: 1) enoxaparin 1 mg/day/12h, or dalteparin 100 U/kg/12h 2) enoxaparin 1-5 mg/kg/day, or dalteparin 200 U/kg/day the first 16 weeks of gestation and 200 U/kg/12h from 16 week

APS= Antiphospholipid Syndrome; **LDA=** Low-Dose Aspirin; **UFH=** Unfractionated Heparin; **LMWH=** Low Molecular Weight Heparin.

Abu-Heija (2014)[14] highlighted the importance of low molecular weight heparin (LMWH) for inactivating aPL by binding LMWH to aPL. This mechanism inhibits aPL and cytotrophoblast cell binding, allowing for its differentiation and invasiveness. Moreover, heparin potentiates Aspirin's effects for preventing the formation of clots and can be used safely during pregnancy. Although the dose of low dose aspirin is well established (81mg/day), the dose of heparin has not been standardized yet; the recommended dose is 5.000U every 12 hours but it may vary according to the stage of pregnancy. In regard to different forms of heparin, substitution of unfractionated heparin (UFH) by LMWH reduces the adverse effects of UFH[11,38,52].

A randomized controlled trial[53] showed that the combined treatment of aspirin and LMWH leads to a significantly high number of livebirths (71%) when compared with aspirin alone (42%)[54]. Despite these results, it is worth mentioning that Farquharson, Quenby, & Greaves (2002)[55] revealed the combination of LMWH with low-dose aspirin did not demonstrate superiority to low-dose aspirin alone (78% and 72% of livebirth, respectively).

In conclusion, although there is still some controversy to the use of aspirin with LMWH/UFH, it should be considered as gold-standard for APS treatment for women during pregnancy and post-partum[2].

3.0. NEW TREATMENTS FOR PREGNANT WOMAN WITH APS

In spite of the advances with current treatment protocols which leads to live birth rates greater than 60.0%, it is noteworthy that new treatments are needed since they do not prevent all complications of APS[56]. Actually, in some cases the women are non-responsive to the established treatment with LDA plus LMWH[57,58].

A large number of new drugs have been reviewed by Chighizola, Ubiali, & Meroni, (2015)[33] as possible future therapies for APS which include clopidogrel, rivaroxaban, statins, molecules that block β2/Anti-β2GP1 antibody binding, molecules that interfere with aPL-induced mediators, rituximab, and other new anticoagulant drugs. However, some cannot be used in pregnancy due to adverse effects or that there are too few studies to adequately assess the risk benefit. Table 3 summarizes the potential new treatments, with hydroxychloroquine being the most promising and easily available. [28]

Table 3. Most promisor treatments of APS in pregnancy

Drug	Related activity	Mode of action	References
Hydroxychloroquine (HCQ)	Antiplatelet Anti-inflammatory Anticoagulant	Reduces of inflammatory cytokines Restore AnxA5	Literature reports safety for woman and fetus[37,47,58–60]
Prasugrel	Antiplatelet	Inhibits platelet $P2Y_{12}$ ADP receptor	A case report of success in live birth[61]
Eculizumab	Anticomplement	Inhibits the complement protein C5	FDA-approved drug for to use in pregnancy[62]
Plasmapheresis and immunoadsorption	aPL reduction	Removes aCL and β2GPI antibodies	A prospective study[63]

AnxA5 = protein Annexin A5; $P2Y_{12}$ ADP = Purinergic Receptor $P2Y_{12}$ Adenosine Diphosphate; aPL = Antiphospholipid antibodies; aCL = anti-Cardiolipin antibody; β2GPI = anti-beta 2 glycoprotein I antibody.

3.1. Hydroxychloroquine (HCQ)

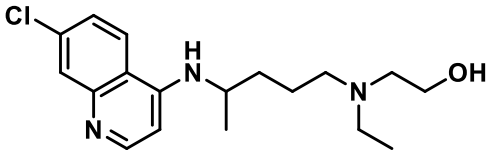
Hydroxychloroquine (figure 2) is an antimalarial drug with antiplatelet, anti-inflammatory and anticoagulant properties. The main mechanism of action involves reduction in the release of inflammatory cytokines such as TNF, IL-1, IL-2, and IL-6 and arachidonic acid from stimulated platelets[37,64–67].

Studies have shown that HCQ can directly inhibit the binding of antiphospholipid anti-β2GPI complexes to phospholipid surfaces[68] which: reduces pregnancy loss[69], restores the placental anticoagulant protein Annexin A5[64,70], and reduces aPL titers in the plasma of SLE-patients with associated APS[71]. Other possible mechanism for its effectiveness involves the reduction in synthesis of auto-antibodies and bypassing the complement system activation[72]. Thus, HCQ is being considered as a possible choice for treatment when the standard protocol (Aspirin/heparin) fails or in selected cases[58].

Additionally, HCQ is usually well tolerated and reduces the need for other concomitant drugs (since HCQ can be administrated with IVIG, dexamethasone, heparin or Aspirin)[47], it has rare adverse effects, and there is no significant risk of bleeding[37,47]. Moreover, children exposed to HCQ during fetal development period showed no teratogenic effects[59,60].

Therefore, the use of HCQ seems to be effective and safe for both the fetus and the woman, randomized controlled trials are needed to establish a standard protocol for its use in association or not with the conventional therapy.

Figure 2. Chemical structure of hydroxychloroquine

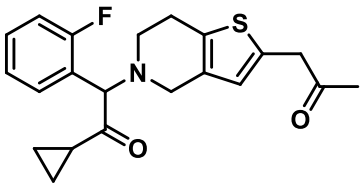


3.2Prasugrel

Prasugrel (figure 3) is a third generation antiplatelet agent from the thienopyridine class, that exerts its effects by binding irreversibly to P2Y12 adenosine diphosphate receptor in platelets[73]. Recently, a case report showed the safe use of prasugrel and Aspirin in a pregnant woman without any complications to the mother and newborn[61]. Although this drug has not been studied for APS treatment in pregnancy, the addition of an antiplatelet agent to standard therapy may possibly protect against recurrent thrombotic events[64].

While this is a single case of a successful live birth using prasugrel, there is limited data available for its use in pregnancy, especially in regard of the safety for APS patients; given that the common side effects involves bleeding during pregnancy and the possibility of teratogenicity. A multidisciplinary team to evaluate each case and whether to combine it or other anti-platelet drugs with other therapies is strongly recommended.

Figure 3. Chemical structure of prasugrel



3.3 Eculizumab

Some authors have found that the complement system is activated when associated with aPL[24]. It was observed, both in *in vitro* and *in vivo* assays, that complement activation, specially C5a, is essential in aPL-induced pregnancy loss and fetal growth restriction[58,74,75]. Eculizumab is a monoclonal antibody developed to inhibit the complement protein C5, preventing the releasing of C5a and C5b, avoiding the membrane attack complex formation[64,76].

Recently, some patients with Catastrophic APS (CAPS), refractory to conventional therapy demonstrated several benefits with the

use of eculizumab which included less thrombotic events and the reversal of thrombocytopenia[77]. It was also been reported that the use of eculizumab in the treatment of severe pre-eclampsia in patients with HELLP (hemolysis, elevated liver enzyme levels, and low platelet levels) syndrome, provided an increase in gestation time and reduction in fetal deaths[78]. These reports lead to new studies for APS treatment once this FDA-approved drug was shown to be safe for use in pregnancy[62].

Nevertheless, it is not clear how eculizumab exerts its effects in pregnant woman and the use in combined therapy needs further evaluation.

3.4. Plasmapheresis and immunoadsorption

More recently, a prospective study was published by Ruffati and coworkes (2016)[63] which proposes the use of LDA and LMWH combined with plasmapheresis and immunoadsorption. These last two treatments have the ability to remove anticardiolipin (aCL) and anti-beta 2 glycoprotein I (β2GPI) antibodies from maternal blood[79]. This combined therapy showed high efficacy and safety since it was possible to achieve a high live birth rate (94.4%) and a small amount of severe pregnancy complications. Although it is effective, this treatment is highly expensive due the procedure that need specific equipment in specialized hospitals, hindering access of patients with low income.

4.0. CONCLUDING REMARKS

Despite many arising therapies, the treatment of APS remains life-long anticoagulation therapy. Pregnancy is not contraindicated in patients with APS, though it is extremely important that a multidisciplinary clinical team has assisted the mother from the outset by planning the best therapeutic approach to minimize the risks for the mother and the fetus.

Although the standard therapy of APS in pregnancy involves the use of Aspirin combined or not with heparin, many reports show that some women are refractory to this treatment. Recently, many drugs have been studied as possible future therapies to APS such as new anticoagulants, molecules anti-aPL complement system inhibitors, anti-inflammatory agents, and B-cell targeted therapies. Nonetheless, a scarce number of drugs were approved for the use during pregnancy. Actually, the innovation for the treatment of APS in pregnancy relies on clinical case reports.

However, new possibilities of treatment for pregnant woman with APS has emerged due to an increase in the number of medical reports and case studies, in addition to advances in the development of new drugs, such as monoclonal antibodies, and novel types of therapies (e.g. plasmaphereses).

Therefore, the development of new therapeutic modalities with other well-designed clinical trials are needed in order to treat and/or prevent thrombosis in pregnant patients with APS and increase the live birth rate.

5.0. CONFLICT OF INTEREST

The author(s) confirm that this article content has no conflict of interest.

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