

Obstetric uses of intravenous immunoglobulin: Successes, failures, and promises

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Intravenous immune globulin (IVIG) is approved for use in a number of conditions that may occur in obstetrical patients, including autoimmune thrombocytopenia and immune deficiency syndromes. IVIG also is widely used in obstetrics for nonapproved indications, such as fetal-neonatal alloimmune thrombocytopenia, antiphospholipid syndrome, and recurrent miscarriage. This review critically analyzes the use of IVIG for these indications based on the best available information. The authors conclude IVIG is effective in the management of fetal-neonatal alloimmune thrombocytopenia. IVIG appears promising as a treatment for severe fetal-neonatal alloimmune hemolysis due to antierythrocyte antibodies. A prospective multicenter trial should be undertaken. IVIG is no more effective than heparin and low-dose aspirin in the treatment of pregnancies complicated by antiphospholipid syndrome but has not been adequately evaluated in refractory cases. Finally, pending convincing studies, IVIG is not effective and should not be used for the management of recurrent miscarriage. (*J Allergy Clin Immunol* 2001;108:S133-8.)

Key words: Intravenous immune globulin, fetal-neonatal alloimmune thrombocytopenia, fetal-neonatal alloimmune hemolysis, antiphospholipid syndrome, recurrent pregnancy loss

Intravenous immune globulin (IVIG) is used in obstetrical patients for a variety of conditions, including FDA-approved indications such as autoimmune thrombocytopenia, as well as a number of nonapproved indications. The use of IVIG in obstetrics for off-label indications appears to be growing, despite the lack of evidence-based efficacy for some conditions. This is problematic because IVIG is an expensive treatment, supplies sometimes are limited, and adverse effects may occur. This review pro-

Abbreviations used

APS: Antiphospholipid syndrome
IVIG: Intravenous immune globulin
Rh D: Rhesus D antigen/antibody

vides a critical analysis of the most common nonapproved obstetric uses of IVIG, with an eye toward the most promising and deserving of study.

FETAL-NEONATAL ALLOIMMUNE THROMBOCYTOPENIA

Alloimmune thrombocytopenia affecting the fetus or neonate is a potentially life-threatening disorder occurring in about 1 in 1000 to 1 in 2000 live births. In this condition, maternal alloantibodies directed against fetal (paternally inherited) platelet antigens arise as a result of feto-maternal transplacental passage of incompatible platelets during pregnancy. Although a number of diallelic, polymorphic platelet antigens may be the cause, the most frequent antigen incompatibility between mother and father is the human platelet antigen-1a (formally known as the PL^{A1} antigen), which results in serious fetal-neonatal thrombocytopenia.

Fetal-neonatal alloimmune thrombocytopenia usually is recognized when an infant is found to have clinical features of moderate to severe thrombocytopenia at birth or soon thereafter. In particularly severe cases, affected fetuses or neonates develop intracranial hemorrhage, a condition that may cause serious morbidity or mortality. This dire complication may occur in up to 20% of reported cases.^{1,2}

The recurrence risk for fetal-neonatal alloimmune thrombocytopenia is estimated at 80% to 90%.^{3,4} It approaches 100% in cases of maternal alloimmunization and known maternal-fetal human platelet antigen-1a incompatibility. This, coupled with the substantial risk for fetal or neonatal intracranial hemorrhage, prompted clinicians to seek strategies for preventing thrombocytopenia resulting in fetal or neonatal morbidity or mortality.

Administering IVIG to the mother during pregnancy is the most successful strategy for increasing the fetal platelet count. In 1988, Bussel⁵ showed that weekly infusions (1 g/kg maternal body weight) beginning at 20 to 24 weeks' gestation would stabilize or increase the fetal platelet count in fetuses with documented alloimmune thrombocytopenia. In a follow-up study of 55 pregnancies with documented fetal alloimmune thrombocytopenia,

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Bussel et al⁶ found that between 62% and 85% of fetuses responded to maternal IVIG, depending on how a response was defined. Importantly, none of the 73 total fetuses treated by Bussel et al with maternal IVIG suffered intracranial hemorrhage, compared with 16 of their untreated siblings.⁷ According to estimates, intracranial hemorrhage will occur in no more than 1 in 100 fetuses managed according to the recommended IVIG protocol. Others have noted similar salutary effects of IVIG on the fetal platelet count.^{8,9} Maternally administered IVIG, therefore, has become the recommended standard treatment of known fetal alloimmune thrombocytopenia.¹⁰

Several nuances of fetal-neonatal alloimmune thrombocytopenia and its treatment deserve mention. First, severe fetal-neonatal hemorrhage may occur in a first pregnancy. Since screening for maternal antiplatelet antibodies is not a part of prenatal care, these first pregnancy cases will be untreated. Second, most experts document fetal thrombocytopenia via umbilical venous blood sampling before beginning IVIG therapy. In doing this, it appears prudent to transfuse the fetus with maternal platelets to prevent umbilical venous bleeding by immediately increasing the fetal platelet count. Third, adding other immunomodulators, such as steroids, to the treatment regimen does not add to the apparent benefit of IVIG.⁶ The direct infusion of IVIG into the fetus also is not as effective as administration to the mother.⁹

FETAL-NEONATAL ALLOIMMUNE HEMOLYSIS (ERYTHROBLASTOSIS FETALIS)

The number of antierythrocyte alloimmunized pregnancies has dropped dramatically since the introduction of anti-D immune globulin. Despite this triumph of science and medicine, fetal alloimmune hemolysis persists as a substantial clinical problem. Severe cases are particularly worrisome, and many of these occur early in gestation when conventional treatment with fetal transfusion is difficult technically.

There are 2 reasons for the persistence of fetal alloimmune hemolysis. First, a small proportion of Rh D-negative women become alloimmunized annually because of failed or forgotten anti-D immune globulin prophylaxis. About 25% of these will have pregnancies complicated by severe fetal hemolytic anemia, resulting in fetal hydrops.¹¹ Second, alloimmunization to non-Rh D erythrocyte antigens (such as Rh E, Rh c, Rh C, Kell, and Fy^a) has emerged as an infrequent, although clinically important, cause of fetal morbidity and mortality.¹² Taking a lead from the apparent success of IVIG in the management of feto-neonatal alloimmune thrombocytopenia, IVIG has been suggested as an adjunctive treatment in severe cases of fetal alloimmune hemolysis, especially when severe hemolysis occurs early in gestation and fetal transfusion is difficult. The exact mechanism is unknown, but several explanations have been offered including feedback inhibition of maternal antibody synthesis, blockade of Fc-mediated antibody placental transport, and blockade of reticuloendothelial Fc-

receptors.^{13,14} Studying antibody titers and blood indices in alloimmunized pregnancies, one group reported no change in fetal hemoglobin concentrations and maternal and fetal antibody titers in IVIG-treated pregnancies in contrast to increased titers and decreased hemoglobin concentrations in untreated cases.¹⁴

Initial reports of IVIG use in women with antierythrocyte alloimmunization were encouraging. Berlin et al¹⁵ reported a favorable outcome using IVIG as an adjunct to plasma exchange, noting that anti-D titers did not increase after IVIG was initiated. Two other groups reported success in 7 of 8 women treated solely with maternal IVIG infusions during pregnancy.^{16,17} Another group¹⁸ found no such benefit in 6 alloimmunized women, however. Maternal IVIG (1 g/kg maternal body weight) did not appear to reduce the total number, frequency, or volume of intrauterine transfusions in severely anti-Rh D alloimmunized pregnancies. Maternal anti-D titers also did not decrease significantly after treatment. Treatment was beneficial in 1 case of Kell alloimmunization. It should be noted that IVIG was not administered until after fetal anemia was demonstrated by cordocentesis, usually after 20 weeks' gestation.

More recently, our group reported that maternal IVIG appeared to be beneficial in the pregnancies of 2 women with histories of severe, early-onset erythroblastosis fetalis that had failed to respond to conventional treatments.^{19,20} Theorizing that early treatment might inhibit fetal red blood cell destruction and delay anemia, we initiated empiric serial IVIG infusions (1 g/kg maternal body weight) during the first trimester, repeating them weekly until delivery. Both women delivered healthy term infants. In 1 case,²⁰ fetal hydrops developed after serial IVIG infusions were discontinued in the third trimester despite continuation of serial fetal blood transfusions. Remarkably, hydrops resolved when IVIG infusions were resumed.

Two groups have compared conventional treatment (intrauterine fetal transfusions) with maternal IVIG in women with histories of severe erythroblastosis fetalis.^{21,22} In the first prospective study, IVIG (0.4 mg/kg daily for 5 days every 2 weeks) was administered to 24 women, 13 of whom had a prior fetal death.²¹ No fetal hydrops or deaths occurred in women treated with serial IVIG infusions and anti-D antibody titers, and amniotic fluid bilirubin level (a measure of hemolysis) measurements dropped dramatically. None of the treated infants needed more than plasmapheresis and/or phototherapy in the neonatal period. In a larger retrospective study, Voto et al²² compared pregnancy outcomes of 30 women who received serial maternal IVIG infusions (1 g/kg maternal body weight) before 20 weeks' gestation and fetal transfusions thereafter with 39 women treated with only fetal transfusions. In the maternal IVIG group, there were fewer patients with a fetal hematocrit below 16% at the first blood sampling (33% vs 52%) and fewer who received more than 2 fetal transfusions (38% vs 50%). Most importantly, there were fewer cases of fetal hydrops (19% vs 80%) and deaths (25% vs 60%) in the IVIG-treated group.

Some investigators have given IVIG directly to the fetus at the time of transfusion in an attempt to limit red blood cell destruction. Results have been disappointing. Dooren et al²³ studied 20 women with severe fetal anemia requiring fetal transfusion and randomly assigned them to either IVIG and transfusion or transfusion alone. They reported no advantage to IVIG use in terms of fetal hemoglobin concentration (2.8 mmol/L vs 2.4 mmol/L) or hematocrit (15% vs 11%). While infants given IVIG in utero required fewer neonatal exchange transfusions (85% vs 100%), more pregnancies in the IVIG group ended in fetal death (30% vs 10%). Likewise, Ulm et al²⁴ found no benefit to direct fetal IVIG administration at the time of transfusion in 12 women, compared with transfusion alone in 22 women. The groups did not differ in terms of fetal or birth hematocrit, the need for neonatal exchange transfusion, or admission to intensive care. None of the women studied appeared to be severely alloimmunized.

In summary, the use of IVIG in antierythrocyte alloimmunized pregnancies may be beneficial by inhibiting maternal antibody synthesis, blocking Fc-mediated antibody transport across the placenta, or limiting fetal red blood cell destruction. Although published trials have yielded mixed results, most groups have reported some benefit when IVIG is administered maternally. A well-designed, multicenter trial to determine the efficacy of IVIG in antierythrocyte alloimmunized pregnancy is needed. In the meantime, empiric use should be limited to unusually severe (and thus infrequent) cases characterized by either (1) antierythrocyte alloimmunization with a history of severe fetal hemolysis (fetal hydrops or fetal death) in spite of conventional treatment with fetal transfusion or (2) a history of early-onset severe anemia (before 20 weeks' gestation) when fetal transfusion is difficult technically.

RECURRENT MISCARRIAGE

Antiphospholipid antibodies (lupus anticoagulant and anticardiolipin antibodies) remain the only scientifically validated immune cause of recurrent miscarriage. Nonetheless, the idea that many women with otherwise unexplained recurrent miscarriage have an aberrant maternal alloimmune response to the semiallogeneic fetus has generated a remarkable amount of interest and controversy. This hypothesis holds that normal pregnancy requires maternal immunologic recognition and an immunosuppressive response to paternally derived antigens expressed by embryo-fetal tissues. In a reversal of traditional alloimmunological thinking, early pregnancy loss is supposed to result when there is a failure of maternal alloimmune recognition of the conceptus. Proponents further hypothesize that alloantibodies and natural killer cells play a role in the immune destruction of pregnancy and the natural alloimmune recognition of pregnancy.

A major problem in the field has been the lack of agreement as to which tests indicate an abnormal alloimmune response to pregnancy and therefore would enable the iden-

tification of women with alloimmune-mediated recurrent miscarriage. Proponents argue that increased peripheral-blood natural killer-cell numbers and the absence of flow-cytometrically identified maternal anti-paternal leukocyte antibodies are relevant markers. Many authorities disagree, and appropriate identification of women with alloimmune-mediated recurrent miscarriage is controversial.

Despite the continuing controversy in this field, IVIG administration is proposed as an immunosuppressive therapy for so-called alloimmune-mediated recurrent miscarriage because of the observation that it contains antibodies that block antibody-mediated immune damage. Other known immunomodulating effects of IVIG include T-cell receptor blockade, inhibition of natural killer-cell activity, inhibition of Th-1 cytokine secretion, Fc receptor blockade, complement inactivation, down-regulation of B-cell responsiveness, and enhanced T-cell suppressor cell function.²⁵ One group reported that IVIG administration resulted in fewer peripheral circulating natural killer cells in patients with recurrent miscarriage,^{26,27} but later reported that the number did not correlate with decidual natural killer-cell activity.²⁸

Few data support the use of IVIG clinically in women who are suspected of having alloimmune-mediated recurrent miscarriage. Once limited to a few case series,^{29,30} 6 randomized, controlled trials and 1 meta-analysis now have been published. Only 1 group reported any benefit.³¹ Women were randomly assigned to receive either 0.5 g/kg monthly of IVIG or placebo, with infusions beginning in the follicular phase of the cycle when pregnancy was desired. A total of 68% of the IVIG-treated women had successful pregnancies compared with only 38% of control women ($P = .04$). The successful pregnancy rate in the untreated group was lower than expected, many of whom had only 2 previous miscarriages.

Other reports have not been as favorable. The double-blinded German RSA/IVIG Group³² study included 64 women with recurrent miscarriage who received either 30 g of IVIG or 5% albumin in the first trimester and 20 g every 3 weeks thereafter until 25 weeks' gestation. A total of 20 of the 33 (61%) in the IVIG group and 21 of 31 (68%) placebo patients had successful pregnancies ($P > .05$). When they excluded 5 chromosomally abnormal abortuses and 2 pregnancies that were lost due to cervical incompetence, there was no difference between the treatment and control groups. Another study³³ randomized 34 women with recurrent miscarriage to receive either a weight-adjusted dose of IVIG or placebo beginning early in pregnancy through 34 weeks' gestation. Infusions were repeated weekly in the early first trimester and every 2 weeks thereafter. A total of 9 of 17 (53%) in the IVIG group and 5 of 17 (29%) in the placebo group had successful pregnancies; this difference was not significant, even after adjustment for number of prior miscarriages.

In an attempt to replicate the protocol in the positive study of Coulam et al,³¹ Stephenson et al³⁴ studied 62 women with 2 or more consecutive, unexplained miscarriages who received either IVIG or placebo starting in the follicular phase. Unlike the study of Coulam et al, this

study was double-blinded. Stephenson et al found no significant difference in the proportions in each group who had a successful pregnancy (58% in the IVIG group vs 56% in the saline controls).

Two other studies have failed to associate IVIG treatment with improvement in successful pregnancy outcomes among women with recurrent miscarriage. Perino et al³⁵ performed a double-blinded, randomized study of IVIG versus placebo in women with 3 or more unexplained, consecutive miscarriages. This study focused on early pregnancy loss with a live pregnancy beyond 12 weeks' gestation as the primary outcome of interest. In this regimen, women were given 25 g IVIG on 2 consecutive days between 5 and 7 weeks' gestation and a third dose 3 weeks later if pregnancy was confirmed sonographically. Of the 22 women in the IVIG group, 16 (73%) pregnancies progressed to or beyond 12 weeks' gestation compared with 20 of 24 (83%) in the placebo group. Overall, 16 of the 22 (73%) IVIG-treated pregnancies and 19 of the 24 (79%) placebo pregnancies produced live births.

In the most recent randomized controlled trial,³⁶ 41 women with a history of 3 or more unexplained losses were given IVIG or placebo, with no significant difference in the proportions of live births (77% vs 79%). There were no differences in the proportions of live births between those women who received IVIG and placebo when women were grouped according to primary recurrent miscarriage (82% vs 89%) and secondary recurrent miscarriage (73% vs 70%).

The only published meta-analysis³⁷ used 4 of the then-published 5 randomized controlled trials and found an overall odds ratio of 1.48 in favor of IVIG. The 95% confidence intervals ranged from 0.84 to 2.60, however, making this effect statistically insignificant. The authors, themselves strong proponents of IVIG therapy, attributed this lack of statistical significance to insufficient statistical power. The addition of the 2 trials^{35,36} published after the meta-analysis indeed would increase the sample size and statistical power. Both of these were negative, however, and would serve to move the odds ratio closer to unity, weakening any salutary effect that IVIG might have on recurrent miscarriage.

With 6 randomized controlled trials published, therefore, the usefulness of IVIG as a treatment for recurrent miscarriage would appear to be limited. Nonetheless, some clinicians continue to treat women with IVIG using varying regimens. This is unjustified scientifically and should be discouraged.

ANTIPHOSPHOLIPID SYNDROME

Antiphospholipid syndrome (APS) is characterized by the presence of circulating antiphospholipid antibodies in association with specific clinical features, which may include thrombosis (either arterial or venous) or adverse pregnancy outcomes, most often fetal loss. Pregnancies that are affected by APS but do not result in fetal loss often are complicated by severe pregnancy-induced

hypertension, fetal growth restriction, or placental insufficiency requiring preterm delivery. Readers should understand that the term antiphospholipid antibodies describes a family of autoantibodies that likely involve a range of target specificities and affinities, but all of which recognize various combinations of phospholipids and/or phospholipid-binding proteins.

The most commonly detected antiphospholipid antibodies are lupus anticoagulant, anticardiolipin antibodies, and anti- β_2 -glycoprotein I antibodies. Because there is no definitive association of specific clinical manifestations with a particular antiphospholipid antibody, multiple tests (most commonly lupus anticoagulant and IgG and IgM anticardiolipin) should be used in seeking the APS diagnosis. Anti- β_2 -glycoprotein I antibodies currently are not included in the international consensus statement on preliminary classification criteria for definite APS,³⁸ but these antibodies are associated strongly with thrombosis and other APS features.³⁹ Many experts believe that internationally standardized anti- β_2 -glycoprotein I antibody assays will replace lupus anticoagulant and anticardiolipin assays for the diagnosis of APS in the near future.

Whether antiphospholipid antibodies per se are the cause of the associated adverse obstetric outcomes is debated. Working with murine models, some investigators found that passive transfer of antiphospholipid antibodies results in clinical manifestations of APS, including fetal loss and thrombocytopenia.^{40,41} The induction of murine fetal loss in this model is variable, however, possibly depending upon factors such as mouse strain, antibody specificity(ies), or model inadequacy, rendering the interpretation of this model system difficult at best. One group has used a murine pinch-induced venous thrombosis model to demonstrate that human polyclonal and murine monoclonal antiphospholipid antibodies are associated with larger and more persistent thrombi than in mice treated with control antibodies.⁴² A variety of mechanisms by which antiphospholipid antibodies may cause thrombosis have been suggested. The most obvious hypothesis is that antiphospholipid antibodies interfere with the normal *in vivo* function of phospholipids or phospholipid-binding proteins that are crucial to the regulation of coagulation. Candidate molecules or pathways that might be adversely affected include β_2 -glycoprotein I (which has anticoagulant properties), prostacyclin, prothrombin, protein C, annexin V, and tissue factor.

Appropriate treatment of women with APS during pregnancy decreases both maternal and fetal morbidity and mortality. Past case series of women with APS were predominantly characterized by the presence of lupus anticoagulant and ≥ 20 IgG phospholipid-binding units of anticardiolipin, and 1 or more fetal deaths, thrombosis, SLE, autoimmune thrombocytopenia, or a combination of these features. Evidence from these cases supported treatment with heparin to improve the outcome of the conceptus.^{43,44} The risks for preeclampsia and placental insufficiency requiring early delivery were substantial, however, with 1 or more of these complications occurring in 50% or more of patients. The risk of maternal

thrombosis or thromboembolism was substantial as well, reaching 12% in 1 case series.⁴⁴ One woman on modest thromboprophylactic doses of heparin died secondary to an apparent embolic stroke.

In 3 recent trials of women with antiphospholipid antibodies, maternal and fetal-neonatal outcomes were more sanguine.⁴⁵⁻⁴⁷ In all trials, women with prior thrombosis or systemic lupus erythematosus were excluded and most women had recurrent preembryonic or embryonic pregnancy loss, rather than fetal loss. One trial included women with either IgG or IgM anticardiolipin (as well as antiphosphatidylserine) antibodies, but excluded women with lupus anticoagulant. The other 2 included women with lupus anticoagulant or anticardiolipin antibodies at any positive level. Two of the 3 trials^{45,46} found the combination of heparin and low-dose aspirin more effective than low-dose aspirin alone for achieving live births. The numbers were quite similar (live births 70%-75% vs 40%-45% in the heparin group vs the low-dose aspirin group, respectively). Adjusted-dose heparin was used in one of these studies,⁴⁵ while low-dose heparin (5000 units of standard heparin twice daily) was used in the other.⁴⁶ In the third trial,⁴⁷ the subjects were randomized to receive either low-dose aspirin or a placebo—no heparin was given. Live birth rates were more than 80% in both the aspirin- and placebo-treated women. Although nearly 25% of the subjects included in this trial had lupus anticoagulant, more than half of the subjects had only low levels of IgG or IgM anticardiolipin antibodies and thus did not qualify as having definite APS.

The results of all 3 trials contrast substantially with the findings of the earlier case series discussed in the preceding paragraph, in that the rates of preeclampsia or placental insufficiency requiring preterm birth were quite low and no women suffered a thrombosis or stroke. The authors of the third trial appropriately emphasize that some women labeled as having antiphospholipid-related recurrent pregnancy loss do not require heparin treatment to have a successful pregnancy.

IVIG also has been used to treat APS pregnancy, usually in conjunction with heparin and low-dose aspirin, and especially in women with poor past histories or recurrent pregnancy loss during heparin treatment. In the largest case series, patients treated with immune globulin, heparin, and aspirin had few pregnancy-related complications.⁴⁸ None of 16 pregnancies had fetal growth restriction, 75% were delivered after 34 weeks' gestation, and only 25% of the patients had preeclampsia. Interestingly, IgG anticardiolipin levels decreased throughout the course of therapy in the 7 treated pregnancies. Similarly, investigators noted no preeclampsia and few preterm deliveries in a small case series of women with APS who were treated with immune globulin.⁴⁹

The seemingly excellent outcomes in a case series of high-risk patients treated with IVIG prompted a pilot randomized, controlled study of pregnant women with APS.⁵⁰ All 16 women had well-characterized APS with lupus anticoagulant and/or medium to high levels of IgG anticardiolipin antibodies. Treatment with IVIG begin-

ning at or before 12 weeks' gestation was compared with placebo (5% albumin). All women also received heparin and low-dose aspirin. IVIG was used at a dose of 1 g/kg body weight for 2 consecutive days each month until 36 weeks' gestation. All patients in the trial had successful pregnancies. There was no difference in obstetric or maternal outcomes between those who were treated with IVIG versus placebo, and the rates of complications were fairly low, although 1 woman had a postpartum deep-vein thrombosis. It appears, therefore, that IVIG is not of significant benefit beyond heparin therapy in the treatment of pregnant women with definite APS. In contrast to the women included in this randomized trial, the apparent excellent outcomes noted in the aforementioned cases series included a substantial number of women who had failed other therapies during pregnancy. Whether the addition of IVIG is beneficial in pregnancy treatment of such refractory cases remains untested.

SUMMARY

Four nonapproved uses of IVIG in obstetrics were reviewed. The use of maternal IVIG in the management of fetal-neonatal alloimmune thrombocytopenia is widely regarded as effective, and treatment of affected pregnancies is considered standard practice in the United States. Preliminary data suggest that maternal IVIG is promising as a treatment for fetal-neonatal alloimmune hemolysis (erythroblastosis fetalis). A strategy that includes appropriate pilot studies and a multicenter randomized trial should be put in place to determine IVIG's use in the management of this condition.

In contrast, the data supporting the use of IVIG in the treatment of recurrent miscarriage are limited to 1 well-designed study, while several other well-designed studies suggest no benefit. The use of IVIG in the treatment of recurrent miscarriage should be abandoned unless a properly designed multicenter trial of sufficient size finds beneficial evidence.

The best study, although limited in size, suggests that IVIG is no more beneficial than heparin in the treatment of APS during pregnancy. Case series suggest that IVIG may benefit women with APS who have failed heparin treatment in a prior pregnancy, however. Again, a multicenter randomized trial will be required to prove the suggested benefit.

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