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Review article

Thrombocytopenia in Patients with Chronic Hepatitis C Virus Infection

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Abstract. Thrombocytopenia in patients with chronic hepatitis C virus (HCV) infection is a major problem. The pathophysiology is multifactorial, with auto-immunogenicity, direct bone marrow suppression, hypersplenism, decreased production of thrombopoietin and therapeutic adverse effect all contributing to thrombocytopenia in different measures. The greatest challenge in the care of chronic HCV patients with thrombocytopenia is the difficulty in initiating or maintaining IFN containing anti-viral therapy. Although at present, it is possible to avoid this challenge with the use of the sole Direct Antiviral Agents (DAAs) as the primary treatment modality, thrombocytopenia remains of particular interest, especially in cases of advanced liver disease. The increased risk of bleeding with thrombocytopenia may also impede the initiation and maintenance of different invasive diagnostic and therapeutic procedures. While eradication of HCV infection itself is the most practical strategy for the remission of thrombocytopenia, various pharmacological and non-pharmacological therapeutic options, which vary in their effectiveness and adverse effect profiles, are available. Sustained increase in platelet count is seen with splenectomy and splenic artery embolization, in contrast to only transient rise with platelet transfusion. However, their routine use is limited by complications. Different thrombopoietin analogues have been tried. The use of synthetic thrombopoietins, such as recombinant human TPO and pegylated recombinant human megakaryocyte growth and development factor (PEG-rHuMDGF), has been hampered by the development of neutralizing antibodies. Thrombopoietin-mimetic agents, in particular, eltrombopag and romiplostim, have been shown to be safe and effective for HCV-related thrombocytopenia in various studies, and they increase platelet count without eliciting any immunogenicity Other treatment modalities including newer TPO analogues- AMG-51, PEG-TPOmp and AKR-501, recombinant human IL-11 (rhIL-11, Oprelvekin), recombinant human erythropoietin (rhEPO), danazol and L-carnitine have shown promising early result with improving thrombocytopenia. Thrombocytopenia in chronic HCV infection remain a major problem, however the recent change in DAAs without IFN, as the frontline therapy for HCV, permit to avoid the dilemmas associated with initiating or maintaining IFN based anti-viral therapy.

Keywords: Hepatitis C, Chronic; Hepatitis C, Chronic/ complications; Hepatitis C, Chronic/ drug therapy; Thrombocytopenia/virology; Thrombocytopenia/drug therapy; Direct-acting antivirals/therapeutic use; Ribavirin/therapeutic use; Interferon-alpha/ therapeutic use.

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Introduction. Chronic hepatitis C virus (HCV) infection affects 3% of the world's population and 1.3% of the United States' population.[1,2] It is a leading cause of chronic liver disease, cirrhosis, and hepatocellular carcinoma, and is one of the most common causes of liver transplants in the United States.[2] Besides hepatic complications, chronic HCV infection is also associated with several extra-hepatic manifestations including thrombocytopenia. Thrombocytopenia in chronic HCV infection is a major problem, particularly in patients with advanced liver disease. The risk of serious bleeding with severe thrombocytopenia can prevent invasive procedures including biopsies for staging.[3] Thrombocytopenia can also complicate bleeding manifestations such as variceal bleeding. It may impede the initiation and continuation of antiviral therapy, potentially decreasing the probability of successful HCV treatment.[4] Recent studies have evaluated the underlying mechanism of thrombocytopenia in chronic HCV infection and assessed the usefulness of several therapeutic options.

Epidemiology. The prevalence and degree of thrombocytopenia increase with the severity of liver disease and correlates to hepatocellular damage and hepatic fibrosis.[5] However, use of varying definition for thrombocytopenia and insufficient data on study characteristics such as age, gender, HCV treatment rates and disease severity preclude a more accurate estimate of the overall prevalence.[6] A systematic review estimated the average prevalence of thrombocytopenia in chronic HCV infection to be nearly 24% (**Table 1**).[6]

Table 1. Prevalence of thrombocytopenia in chronic hepatitis C infection.

Author	Study Design	Total cases in study	Platelet counts (X 10^9)	Cases with cirrhosis (%)	Cases receiving Anti-viral therapy (%)	Cases with thrombocytopenia (%)
Ikeda et. al[70]	Cohort	1056	140-150	9.7	8.2	38.7
Moriyama et. al [71]	Cohort	645	140-150	NR	0.0	29.2
Nagamine et. al [72]	Cross-sectional	368	140-150	0.0	NR	41.0
Ordi-Ros et al. [73]	Cross-sectional	230	140-150	11	8.3	18.3
Poynard et al. [74]	Cross-sectional	1354	140-150	NR	0.0	31.1
Sylvestre et al. [75]	Cross-sectional	409	140-150	NR	NR	31.1
Shanmuganathan et al.[76]	Cross-sectional	182	140-150	9.9	NR	28.0
Taliani et al. [77]	Cross-sectional	78	140-150	48.7	0.0	44.8
Borroni et al. [78]	Cross-sectional	228	130-140	13.2	0.0	9.6
Dalekos et al. [79]	Cohort	75	130-140	NR	NR	13.3
Kaul et al. [80]	Cross- sectional	264	130-140	3.3	Nr	28
Luo et al. [81]	Cross- sectional	111	130-140	20.7	NR	28.9
Prieto et al. [82]	Cross-sectional	100	130-140	25	16	45
Romagnuolo et al. [83]	Cross-sectional	54	130-140	7.4	0.0	24.1
Zachou et al. [84]	Cohort	174	130-140	20.7	30.0	31.2
Hu et al. [85]	Cohort	112	100-130	100	43.8	30.3
Kim et al. [86]	Cross Sectional	141	100-130	7.4	NR	24.8
Renou et al. [87]	Cross Sectional	110	100-130	12.7	0.0	18.2
Cicardi et al. [88]	Cohort	360	<100	24	0.0	16.4
Nahon et al. [89]	Cohort	97	<100	100	NR	45.4
Wang et al. [90]	Cross Sectional	140	<100	5.0	NR	15.7

Mechanism. The pathophysiology of thrombocytopenia in patients with HCV infection is thought to be multifactorial. Besides inducing an autoimmune reaction with production of anti-platelet antibodies, the virus also causes direct bone marrow suppression with resulting thrombocytopenia.[7-10] Chronic HCV infection induced liver fibrosis and cirrhosis leads to portal hypertension with subsequent hypersplenism and sequestration of platelets, decreased the production of thrombopoeitin, and endothelial dysfunction, all of which can contribute to thrombocytopenia.[11-14] Although uncommonly used in developed countries, interferon (IFN) and ribavirin used as part of anti-HCV therapy can also contribute to low platelet count.[15]

Impact on Clinical Management. Although thrombocytopenia in chronic HCV infection is typically low grade and not life-threatening, it represents an obstacle to different diagnostic or therapeutic modalities and may preclude the use of anti-viral treatment.

The greatest challenge in the care of chronic HCV patients with thrombocytopenia is the difficulty in initiating or maintaining IFN containing anti-viral therapy. Although this challenge can be avoided with the use of sole DAAs as the primary treatment modality, thrombocytopenia remains of particular interest, especially in cases of advanced liver disease. In a study by Wang et al., baseline thrombocytopenia increased the risk of drug cessation. Patients with baseline thrombocytopenia actually exhibited compromised sustained virologic response (SVR) rates while those with acquired thrombocytopenia did not. Thus, use of growth factors to maintain SVR rate would be beneficial in those with baseline thrombocytopenia rather than in those who acquire it during therapy as dose reduction doesn't decrease SVR in such cases.[16]

Thrombocytopenia in HCV may also be a problem for patients with baseline platelet count of <50.000/mm^3, particularly in the presence of previous bleeding even when they are treated with DAAs. However, patients with thrombocytopenia and fibrosis have attained >90% SVR with DAAs even if in a proportion lower in respect to patients with a normal platelet count. Thus, DAAs may be continued most of the times without interruption and thrombopoietin mimetics would be helpful only with severe thrombocytopenia (such as a platelet count of <25,000/mm^3).[17-19]

Directly-acting antivirals (DAAs): Recently updated World Health Organization guidelines recommend that DAA regimens (including simeprivir, grazoprevir, daclatasvir, ledipasvir, and sofosbuvir) be used for the treatment of persons with hepatitis C infection rather than regimens with pegylated interferon and ribavirin.[16] Combinations of 2 or 3 DAAs have been shown to be highly effective and safe in both cirrhotic and non-cirrhotic patients in different phase III clinical trials and large real life cohorts with providing SVR rates of >95%. While headache, diarrhea, fatigue, and nausea have frequently been observed, hematologic abnormalities including thrombocytopenia were reported in no more than 1% of cases.[17,18] Lee et al. reported that DAA therapy in one patient precipitated ITP refractory to various treatment modalities and it required several weeks of therapy with multiple platelet transfusions, intravenous immunoglobulin, steroids and romiplostim to achieve a stable platelet count of 40,000/mm^3 with no signs of bleeding.[19] However, this is only one case describing any relation of DAA with thrombocytopenia. A study by Forns et al. showed that HCV genotype 1a-infected patients with surrogate markers of portal hypertension or impaired liver function such as thrombocytopenia and hypoalbuminemia at baseline achieved high SVR rates with ombitasvir/paritaprevir/ritonavir and dasabuvir with ribavirin and treatment was well tolerated.[20] Additionally, reduction in liver fibrosis markers such as fibrosis-4 score and aspartate transaminase platelet ratio along with regression of transient elastography have been reported with use of DAAs in chronic hepatitis C.[21] In any case, by the time, thrombocytopenia improves following SVR obtained with any antiviral therapy among chronic HCV infected patients with advanced hepatic fibrosis.[21,22]

INF based antiviral therapy: Although IFN based antiviral therapy is uncommonly used in developed countries nowadays, the prohibitive cost of DAA may require the use of INF based therapy along with the addition of thrombopoietin mimetics, if required, in economically disadvantaged areas. Additionally, in chronic hepatitis C cases treated with pegylated INF plus

ribavirin, single nucleotide polymorphisms at or near the IL-28B gene have been shown to be a predictor of SVR.[23,24] The American Gastroenterological Association recommends dose reduction of INF with a platelet count between 25,000-50,000 and withdrawal of INF-based treatment with a count below 25,000.[25] This is important because the antiviral therapy itself may cause a further drop in platelet count.[26] Studies have shown IFN-based therapy to cause severe thrombocytopenia in up to 13% of patients, with the incidence higher in patients with lower baseline platelet count.[27,28] The modifications in IFN-based therapy have potential to lower the chances of attaining SVR. The increased risk of bleeding may also impede the initiation and maintenance of different invasive diagnostic and therapeutic procedures such as liver biopsy, variceal banding, paracentesis and thoracentesis, central line insertion, endoscopy and elective surgery.

Management. Various pharmacological and non-pharmacological therapeutic options are available for the management of thrombocytopenia in chronic HCV infection (**Table 2**). These treatment modalities vary in their effectiveness and adverse effect profiles. The most practical strategy in treating HCV-related thrombocytopenia is based on the principle that eradication of HCV infection may result in remission of thrombocytopenia. By eradicating HC virus, DAAs are supposed to improve thrombocytopenia related to hepatitis C infection but may not ameliorate thrombocytopenia related to cirrhosis or portal hypertension. In cases of IFN based antiviral therapy, the usual approach is to continue with the therapy, reducing the dose if platelet count drops below 50,000 cells/μL or discontinuing it for a platelet count of below 25,000 cells/μL.[25] The measures described below are mostly supportive. As expected, there is a lot of published data on how these measures might be necessary to IFN-based therapy but not to them with DAAs.

Platelet transfusion: Though widely used for the management of thrombocytopenia, platelet transfusion has several limitations, especially in patients with chronic liver disease. The increase in platelet count is transient, and hence useful only for procedures or during bleeding. Patients are also at risk for transfusion-related complications, which can occur in up to 30% of the recipients and include viral or bacterial infection, febrile non-hemolytic reactions, and iron overload.[29] Nearly half of all patients undergoing multiple platelet transfusions can develop platelet refractoriness secondary to human leukocyte antigen (HLA) alloimmunization.[30,31] It may not always ensure maintenance of homeostatic platelet levels.[32] Besides, the requirement of hospitalization and high cost may be prohibitive in a resource-poor setting.

Splenectomy and splenic artery embolization: Splenectomy and splenic artery embolization have been used to correct thrombocytopenia in patients with hypersplenism, producing significant and persistent increases in platelet count.[33,34] Akahoshi et al. studied the effect of splenectomy in patients with HCV-associated thrombocytopenia and found above 200% rise in mean platelet count at 1 month after splenectomy.[35] In cases of IFN-based antiviral therapy, the positive effect is known to persist even after the initiation of antiviral therapy, with the mean platelet count nearly 80% above baseline after 12 months of the therapy. Splenectomy, however, is an invasive procedure with high risk of bleeding, sepsis and portal vein thrombosis. Asplenic patients are susceptible to overwhelming post-splenectomy infection. Splenic artery embolization may be an alternative option. In a study by Barcena et al., the mean platelet count increased by 342% from the baseline after 12 weeks of partial splenic artery embolization.[36] Splenic artery embolization, though associated with lower morbidity and mortality than splenectomy, is not free of complications.

Pharmacotherapy: Steroids: With HCV reported to play a pathogenic role in some cases of immune thrombocytopenic purpura, there have been case reports of significant improvement in HCV-related thrombocytopenia with the use of corticosteroid.[37] As described earlier, Lee et al. described a case of resistant ITP which developed after DAA therapy and did not respond to high dose prednisone.[20] Lebano et al. reported a case where the platelet count increased by 175% from baseline six months after steroid therapy and improved further (360% above baseline) after another six months of IFN and ribavirin.[37] Despite similar reports of steroids causing a variable rise in platelet counts, they are not routinely considered in the management of

Table 2. Management of hepatitis C-related thrombocytopenia.

Author/Study	Year	No. of patients	Baseline platelet, mean or median (range)	Intervention	Mean/median platelet count after the intervention	Major complications
Akahoshi et al. [35]	2011	100	56,000 (22,000 – 75,000)	Splenectomy followed by PEG-IFN+RBV	105,000 (range 40,000 – 140,000) at 6 months	Portal vein thrombosis (7%), Wound infection (4%), Bleeding (2%)
Barcena et al. [36]	2005	3	44,067 (39,900– 50,300)	Partial splenic artery embolization	195,000 (128,000 - 243,000) at 12 months	
McHutchison et al. [56]	2007	74	55,000 (26,000 – 94,000)	PEG-IFN/ Ribavirin plus Eltrombopag vs. placebo	Median increase of 31,000 or 54,000 (depending on the dose of Eltrombopag) vs. Median decrease of 25,000	Headache (21%), Dry mouth (11%) Abdominal pain (7%), Nausea (7%)
Afdhal et al./ ENABLE-1 [57]	2014	715	59,0000	PEG-IFN2a / Ribavirin plus Eltrombopag vs. placebo	86,000 vs. 40,000 at 45 weeks	Thrombo-embolic events (3% vs 1%); Hepatic decompensation (10% vs 5%)
Afdhal et al./ ENABLE-2 [57]	2014	805	59,000	PEG-IFN2b/ Ribavirin plus Eltrombopag vs. placebo	105,000 vs. 55,000 at 45 weeks	Thrombo-embolic events (4% vs 0.4%); Hepatic decompensation (10 vs 5%)
Moussa et al. [52]	2012	35	31,000 (21,000-46,000)	Romiplostim	46,000 (range 26,000 – 88,000) at 3 months (2 months after stopping treatment)	
Alvarez et al. [91]	2011	49	69,067 (34,000 – 88,200)	Danazol plus IFN plus Ribavirin	121,081 (range 46,000 – 216,000)	Anemia (40%), Headache (38%) Arthralgia (31%), Myalgia (31%) Malaise (29%), Nausea (26%), Hyposthenia (24%)
Malaguarnera et al. [92]	2011	69	384,000 vs. 412,000	PEG-IFN + RBV with or without L-carnitine	298,000 vs. 327,000 at 12 months	
Lawitz et al. [65]	2004	20	143,000 (43,000 – 244,000)	Recombinant human IL-11 (Oprelvekin)	Median of 198,000 at 45 weeks	Edema of lower extremities (100%)

thrombocytopenia in HCV infection because of the possible risk of worsening viral loads and liver damage.[38,39]

Thrombopoietin analogue: Thrombopoietin (TPO) is a cytokine predominantly synthesized by the hepatocytes in the liver and plays a central role in thrombopoiesis. It binds to TPO receptors (mpl) expressed on the surface of megakaryocyte precursor cells and megakaryocytes, activating signal transduction cascades that result in proliferation and maturation of megakaryocytes.[40] A better understanding of TPO and its role in platelet production and function has led to newer treatment modalities. Synthetic thrombopoietins such as recombinant human TPO and pegylated recombinant human megakaryocyte growth and development factor (PEG-rHuMDGF) cause an increase in platelet count.[41,42] However, their use has been hampered by the appearance of neutralizing antibodies that cross-reacts with both recombinant and endogenous TPO.[43] In a study using PEG-rHuMDGF injection by Li et al., an initial rise in platelet count was followed by the development of an antibody against TPO, detected as early as 56 days after the initial injection.[44] This was associated with corresponding fall in platelet count and a marked decrease in bone marrow megakaryocytes, with an average nadir platelet count of 6% to 8% of baseline.

Thrombopoietin-mimetic agents, in particular, eltrombopag and romiplostim, have been shown to increase platelet count without eliciting any immunogenicity.[45-47] Romiplostin is a peptibody composed of four TPO mimetic peptides attached by glycine bridges to the heavy chain portion of immunoglobulin G. It acts by dimerizing the TPO receptor via its paired peptides, which stimulates platelet production.[48] It is given by weekly subcutaneous injections. Various clinical trials in patients with chronic immune thrombocytopenic purpura have shown romiplostin to cause a dose dependent increase in platelet count, resulting in lower rates of treatment failure, decreased the need for splenectomy and improved quality of life.[49-51] Lee et al. described romiplostim use in a case of resistant ITP after DAA therapy.[20] A study by Moussa et al. in 35 patients with chronic liver disease and thrombocytopenia secondary to HCV

infection showed more than three-fold increase in mean platelet count from the baseline after 3 weeks of therapy.[52] And the mean platelet count remained 1.5 times above the baseline even after 2 months of stopping the drug. Similarly, Voican et al. reported two cases where romiplostin was used to control severe thrombocytopenia; this allowed anti-HCV treatment with pegylated-IFN and ribavirin to be completed successfully without any dose reduction or discontinuation.[53]

Eltrombopag, an orally active TPO agonist, interacts with the trans-membrane domain of the thrombopoietin receptor, activating JAK2/STAT signaling pathways and increasing proliferation and differentiation of human bone marrow progenitor cells into megakaryocytes.[54] Preclinical studies have shown the binding site on the receptor and the signal transduction mechanism to be different for eltrombopag as compared to thrombopoeitin, causing the two to have an additive effect on platelet production.[55] Eltrombopag has been found to be safe and effective in the management of HCV-related thrombocytopenia.[56,57] In a phase II trial,[56] 71-91% of the patients receiving eltrombopag had a dose dependent increase in their platelet counts to levels which allowed initiation of antiviral therapy. 36-65% of patients in the eltrombopag group completed first 12 weeks of antiviral therapy compared to 6% in the placebo group. Though platelet counts decreased during the antiviral treatment phase despite the use of eltrombopag, the count consistently remained above baseline as well as above the level at which a reduction in the pegylated-IFN dose is recommended (<50,000 per cubic millimeter). Another phase III trial, Eltrombopag to Initiate and Maintain Interferon Antiviral Treatment to Benefit Subjects with Hepatitis C-Related Liver Disease (ENABLE-1 and ENABLE-2), showed a higher rate of sustained virological response with the use of eltrombopag than placebo (23% vs. 14%, p = 0.0064 in ENABLE-1 and 19% vs. 13%, p = 0.0202 in ENABLE-2).[57] Pegylated-IFN was administered at higher doses, with fewer dose reductions in the eltrombopag group. Throughout the antiviral treatment, a platelet count of 50,0000 per cubic millimeter or higher was maintained in more patients receiving eltrombopag than placebo (69% vs. 15% in ENABLE-1 and 81% vs. 23% in ENABLE-2).

The most common side effect with these thrombopoietin-mimetic agents is a headache, with the reported incidence in clinical trials ranging from 7% to 21%.[49-51,56,57] Eltrombopag also commonly causes dry mouth, abdominal pain, and nausea, and may be associated with hepatic decompensation like ascites and hepatic encephalopathy.[56,57] Romiplostin may be associated with increased deposition of reticulin in the bone marrow, and possibly marrow fibrosis.[58] The risk of thromboembolic events like portal vein thrombosis is seen with all these agents.[57,58]

Other newer drugs currently under investigation include the peptidic compounds like AMG-531 and PEG-TPOmp, non-peptidic compound like AKR-501, and monoclonal antibodies. AMG-531, a TPO agonist, has been designed with no sequence homology to human TPO to reduce the likelihood of an anti-TPO immune response. Phase II and III studies in ITP patients have shown promising early results with a dose-dependent increase in platelet count with no serious adverse events.[59,60] PEG-TPOmp is a pegylated TPO peptide agonist and has shown to be effective in animal studies. Similarly, AKR-501 is an orally active TPO agonist and has been shown to be effective in clinical studies involving healthy volunteers.[60] In vitro studies have shown engineered monoclonal antibodies to bind mpl and activate TPO-expressing cell lines.[61] However, all these compounds and drugs need further clinical studies, including in patients with HCV and chronic liver disease before they can be considered for routine use.

Cytokines with thrombopoietic potential: Cytokine such as interleukin-11 (IL-11) has thrombopoietic activity. Recombinant human IL-11 (rhIL-11, Oprelvekin), approved for the management of chemotherapy-related thrombocytopenia, has also been shown to increase platelet count in chronic HCV infection.[62-64] In a study by Lawitz et al., use of rhIL-11 (Oprelvekin) in patients with advanced liver disease associated with chronic HCV infection caused a 38% increase in mean platelet count from baseline after 12 weeks of therapy, along with an improvement in the mean Knodell Histology Activity Index from 7.3 to 5.9 (p= 0.006).[65] However, the platelet level tends to fall back on discontinuing the drug.[62] It also causes fluid retention in most patients, and this can be a significant management problem in patients with decompensated cirrhosis.[64]

Erythropoietin: The amino-terminal domain on TPO, which binds to thrombopoietin receptor shares significant homology with erythropoietin. Recombinant human erythropoietin (rhEPO) has shown promising results in improving thrombocytopenia in cirrhotic patients.[66,67] Pirisi et al. studied the effect of rhEPO on the platelet count in 19 patients with thrombocytopenia related to chronic liver disease, and found an increase in mean platelet count by 45% from the baseline in the treatment group as compared to 0% in the placebo group ($p < 0.02$).[67] As rhEPO has also been suggested for the treatment of ribavirin-induced anemia in patients with HCV, this provides the possibility of using a single drug for the treatment of both thrombocytopenia and anemia related to the INF-based antiviral therapy. However, further studies are needed to confirm this.

Danazol: Danazole used in immune thrombocytopenic purpura may have a role in HCV-related thrombocytopenia. In a study by Alvarez et al., the use of danazol along with the anti-HCV treatment resulted in a 75% increase in the mean platelet count from the baseline and allowed 90% of the patients to complete their antiviral treatment.[68] Anemia, headache, arthralgia and myalgia were some of the common adverse effects of the combination therapy reported in the study.

L-carnitine: L-carnitine is a nutrient synthesized from amino acids lysine and methionine. In a study, the addition of L-carnitine to pegylated-IFN-α plus ribavirin resulted in a decrease in the incidence of thrombocytopenia during antiviral therapy.[69]

Conclusions. Thrombocytopenia in chronic HCV infection has a multifactorial pathophysiology and remains a major problem. The recent change in DAAs without IFN, as the frontline therapy for HCV, permit to avoid the dilemmas associated with initiating or maintaining IFN based anti-viral therapy.

DAAs, with high SVR and less than 1% of hematological adverse effects, have been shown to improve thrombocytopenia associated with HCV infection as well as advanced hepatic disease. While eradication of HCV infection itself is the most practical strategy for the remission of thrombocytopenia, various pharmacological and non-pharmacological therapeutic options, which vary in their effectiveness and adverse effect profiles, are available. Thrombopoietin-mimetic agents like eltrombopag and romiplostim have been shown to be safe and effective for HCV-related thrombocytopenia in various studies.

Studies of the long-term effects of DAA on extrahepatic consequences of HCV infection are in progress.

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