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Review Article

Pharmacological Management of Portal Hypertension: A Review Article

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ABSTRACT

Background: Portal Hypertension is considered an abnormal elevation of pressure in the veins that drain blood from the visceral organs (e.g., the spleen) to the liver. This occurs due to elevated resistance to blood flow in the portal circulation with the development of collateral circulation to carry portal blood. Reducing portal pressure and avoiding portal hypertension-related problems are the goals of the pharmacological management of portal hypertension. Portal blood flow and hepatic vascular resistance determine portal pressure. We aimed to present an insight into the pharmacological management of portal hypertension. **Conclusion:** The main goals of current medications in portal hypertension are to either reduce the formation of collateral circulation, hyperdynamic circulation, vascular hyperplasia, renin-angiotensin-aldosterone system (RAAS) activation or to inhibit angiogenesis and fibrosis in the liver to decrease intravascular resistance. Portal hypertension causes splanchnic and systemic arterial vasodilation, which in turn activates the neurohumoral (increase in sympathetic activity and activation of the RAAS) and vasoconstrictive systems; this leads to increased cardiac output, increased blood volume and sodium and water retention. Activation of the RAAS raises portal pressure, according to multiple investigations in cirrhotic animals and patients.

Keywords: Pharmacology, Management, Portal Hypertension

INTRODUCTION

Portal Hypertension is considered an abnormal elevation of pressure in the veins that drain blood from the visceral organs (e.g., the spleen) to the liver, which occurs as a result of elevated resistance to blood flow in the portal circulation with the development of collateral circulation to carry portal blood. Portal hypertension is the pathological elevation of the portal pressure, which normally ranges from 7 to 10 mmHg [1]. Free hepatic venous pressure is an estimate of systemic venous pressure, whereas Wedged Hepatic Vein Pressure (WHVP) represents pressure within the portal venous system. A catheter-measured hepatic venous pressure gradient (HVPG) is the computed difference between the hepatic vein's wedged and free venous pressures. A portal hypertension gradient greater than or equal to 5 mm Hg is deemed abnormal. Pressure gradients between 5 and 9 mmHg are thought to represent subclinical cases of portal hypertension, but gradients more than 10 mmHg are deemed clinically significant [2].

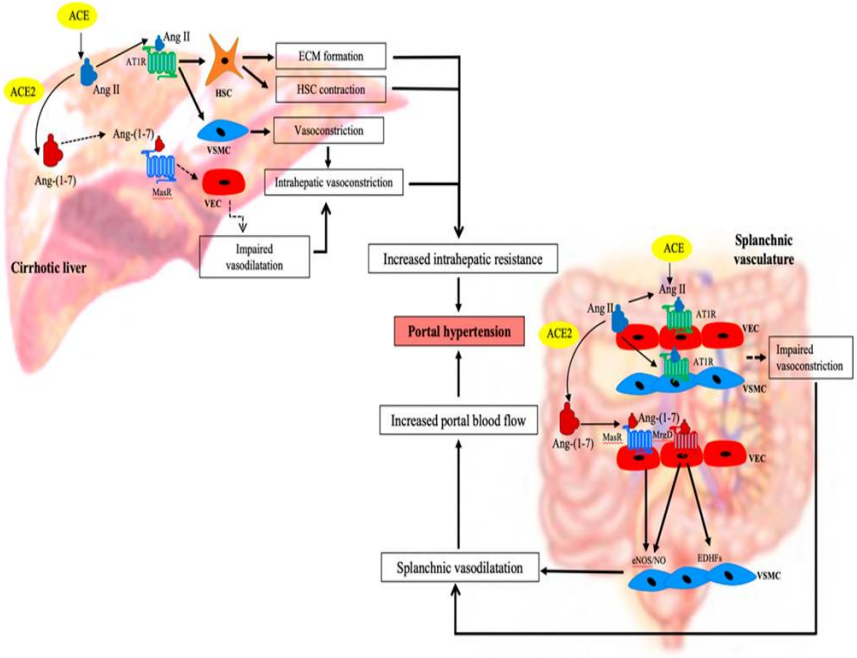
Pathophysiology of portal hypertension

(A)Increased Intrahepatic Vascular Resistance:

(1) Activated hepatic stellate cells (HSCs)

Extracellular matrix (ECM) overproduction is caused by factors that encourage the creation of scar tissue, which replaces functioning liver tissue with fibrous matrix [3]. Vascular smooth muscle cells (VSMCs) and activated HSCs contract to raise hepatic resistance and this contraction is controlled by various vasoconstrictors. Cirrhotic livers produce more angiotensin II (Ang II), a potent RAS peptide with vasoconstrictor action that binds to Ang II type 1 receptor (AT1R) on hepatic stellate cells, leading to increased proliferation of HSCs and sinusoidal

vasoconstriction. Cirrhotic rat livers had an increased AT1R, which led to a vasoconstrictive response to Ang II that increased hepatic vascular tone and resistance [4].



Figuer (1): Role of the renin angiotensin system in cirrhotic portal hypertension [16].

(2) Liver sinusoidal endothelial cells (LSECs)

Liver sinusoidal endothelial cells (LSECs) are a specialized form of endothelial cell distinct from vascular endothelial cells in their structure. Open fenestrations and the lack of an endothelial basement membrane are the defining morphological characteristics of LSECs [5]. These fenestrations are grouped in the cytoplasm to help move substances from the space of Disse and the lumen (sinusoidal space) into the parenchyma. Changes in the fenestrations' diameter and frequency on LSECs are associated with various liver disorders, poisons and traumas. These changes can also lead to a reduction in the liver's overall function**.** Additionally, by actively adapting to changes in intrahepatic blood flow and pressure, these cells preserve the hemodynamics of liver capillaries [6]. In the early stages of a fibrotic liver, a process known as capillarization, liver injuries leading to fibrosis cause loss of LSECs fenestration and formation of basement membrane in the space of Disse. Fibrosis is accompanied by several secretory alterations that contribute to portal hypertension in the liver, including increased endothelin-1 expression and decreased endothelial nitric oxide synthase (eNOS) activity [7].

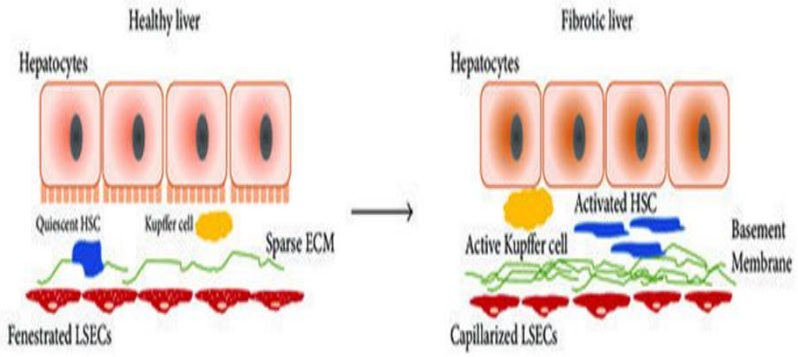


Figure (2) liver sinusoidal endothelial cells (LSEC) morphological alterations during liver fibrosis. In a healthy liver, the space of Disse, which contains very little extracellular matrix (ECM), separates hepatocytes from liver sinusoidal endothelial cells. Disse's space is inhabited by quiescent hepatic stellate cells. The Kupffer cells shift phenotypically, becoming more pro-inflammatory. Solute transport is enabled by the fenestrations on LSECs. Stellate cells become active in a fibrotic liver, the endothelium forms a basement membrane, and the LSECs become defenestrated [16].

(3) Gastrointestinal tract microorganisms

The gut and liver are anatomically related by portal circulation. The liver is continuously exposed to microbial products, food-derived antigens, poisons, nutrients and germs from the gastrointestinal system. Bacterial translocation is a common factor in the development of hepatic encephalopathy, spontaneous bacterial peritonitis and upper gastrointestinal bleeding, three consequences of liver cirrhosis. The inflammatory reaction that results from bacterial translocation causes a rise in portal hypertension, which exacerbates the patients' hyperdynamic circulation [8].

(4) Decreased vasodilators

One of the most significant contributing causes to the rise of intrahepatic vascular resistance is a deficiency in the intrahepatic bioavailability of the endogenous vasodilator nitric oxide (NO). Two mechanisms cause the reduced NO: First, negative regulators (such as caveolin-1), which are up-regulated during cirrhosis, inhibit the NO-generating enzyme endothelial eNOS; as a result, NO production declines [7]. Second, cirrhosis is associated with elevated oxidative stress. The endogenous toxicant peroxynitrite is formed when NO and enhanced superoxide radicals react spontaneously in cirrhosis. This reduces the bioavailability of NO, a vasodilator. Numerous substancesthat cause cirrhosis, including ethanol, viruses, bacteria endotoxins and medications, can cause oxidative stress in LSECs [8].

(5) Increased vasoconstrictors

In addition to vasodilators being reduced in cirrhosis, there is a rise in vasoconstrictors, such as thromboxane A2 (TXA2). TXA2 is generated in LSECs by COX-1 activity. Another significant vasoconstrictor that increases intrahepatic vascular resistance is endothelin 1, which binds to its receptors on HSCs [7].

(B) Increased portal blood flow:

Cirrhotic splanchnic vessels, in contrast to the hepatic vasculature, undergo vasodilatation as a result of intrinsic vascular hypercontractility and localized over-production of vasodilators, resulting in elevated blood flow through these veins [4]. eNOS mainly causes the excess production of NO in splanchnic arteries. NO is produced by endothelial cells and diffuses into VSMCs, where it directly induces the release of cyclic guanosine monophosphate (cGMP) from guanosine triphosphate by membrane-bound soluble guanylate cyclase. Following this, cGMP causes K+ efflux. Additionally, it activates protein kinase reliant on cGMP, which dephosphorylates myosin light chain kinase and causes vasodilatation [4]. Despite the development of portosystemic collaterals, systemic arterial vasodilation leads to increased splanchnic blood flow to the portal system and consequently, higher portal pressure [4]. This illness exacerbates portal hypertension and promotes hyperdynamic circulation, defined as lower peripheral resistance, greater cardiac index, lower mean arterial pressure and lower systemic vascular resistance. Combined with increased blood flow to portosystemic collaterals, hyperdynamic circulation leads to clinically severe consequences such as gastric varices [10].

Pharmacological management of portal hypertension

Reducing portal pressure and avoiding portal hypertension-related problems are the goals of the pharmaceutical management of portal hypertension. Portal pressure is determined by portal blood flow and hepatic vascular resistance [8]. Medications for elevated liver blood flow are currently focused on lowering intravascular resistance through blocking angiogenesis, fibrosis and regenerative nodules or on lowering hyperdynamic circulation, vascular hyperplasia, activation of the renin-angiotensin-aldosterone system and the development of collateral circulation. Portal hypertension causes splanchnic and systemic arterial vasodilation; this leads to increased cardiac output, salt and water retention, and blood volume [9].

(1) Non selective beta-blockers (NSBBs)

Since the early 1980s, nonselective beta-blockers have been the most widely prescribed medications for the treatment of portal hypertension in cirrhosis. NSBBs are still advised for long-term management of portal hypertension [10].NSBBs like propranolol and nadolol have a similar affinity for β1 and β2 in contrast to cardio-selective beta-blockers whose

affinity is specific for β1 (placed in cardiac muscles). Portal pressure is reduced when β1 and β2 are blocked [11], causing a lowering of cardiac output and splanchnic vasoconstriction (unopposed alpha-adrenergic action), respectively. Another NSBB called carvedilol also inhibits α1-adrenergic receptors (Figure 3). This lowers intrahepatic resistance, leading to a larger fall in portal pressure [12].

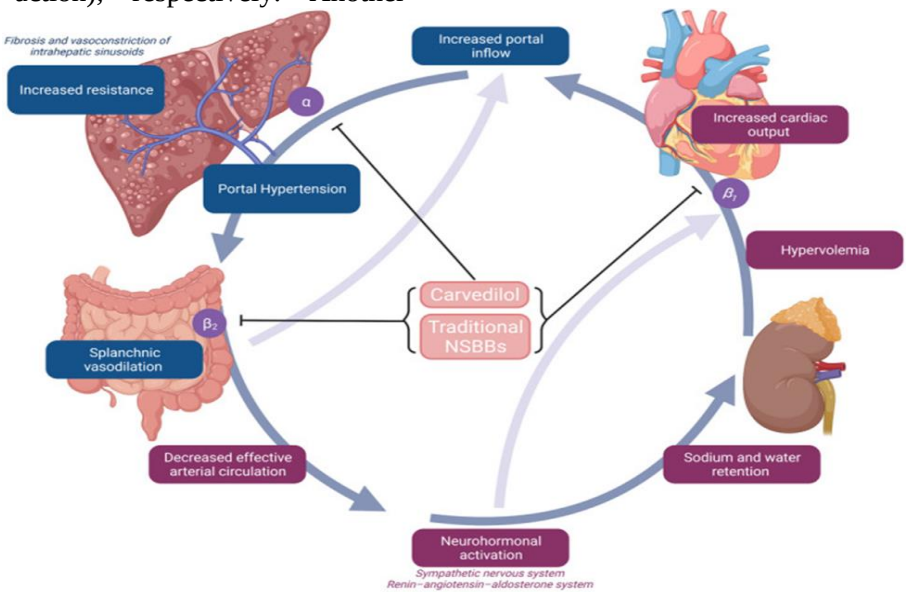


Figure (3): The effects of Nonselective beta blockers in portal hypertension [12].

In addition to the anatomical connection between the two organs through portal circulation, the gut-liver axis is a functional unit that allows the two systems to work together. The liver is in continual contact with various substances, including nutrients, poisons, antigens found in food, byproducts of microbes and microbes found in the gastrointestinal system. A number of problems, including hepatic encephalopathy, upper gastrointestinal hemorrhage and spontaneous bacterial peritonitis, can develop in patients with liver cirrhosis, and bacterial translocation is a prevalent factor in their development. Intestinal transit time is decreased by NSBBs, which in turn reduces bacterial overgrowth. As a result, bacterial translocation, inflammatory response and spontaneous bacterial peritonitis may be prevented. Research has demonstrated that NSBBs can improve long-term survival and reduce the recurrence of variceal hemorrhage [13].

Approximately 5% of individuals experience severe side outcomes that necessitate stopping NSBB, such as heart failure and bradycardia. In addition, 15% of patients are thought to stop taking NSBBs because of less serious side effects such as exhaustion, dyspnea, and sexual dysfunction. Because they greatly reduce quality of life and require a good explanation for the risk-benefit ratio to guarantee their safety, these side events are typically the most concerning for patients on chronic medication [14].

(2) Angiotensin antagonists:

The renin-angiotensin-aldosterone system (RAAS) regulates blood pressure, vascular resistance, salt and water balance and tissue rebuilding after trauma. Antagonists and angiotensin-converting enzyme inhibitors (ACEIs) have been investigated as possible antifibrotic therapies for liver disease due to the elevated serum Ang II concentration reported in cirrhosis patients. This increased concentration is involved in the activation and phenotypic transformation of hepatocyte stem cells (HSCs) into active myofibroblasts, the agents responsible for tissue fibrosis [15]. Angiotensin II (Ang II), a vasoconstrictor peptide, signals through its receptor, the Ang II type 1 receptor (AT1R), in activated hepatic stellate cells (HSCs), leading to the deposition of extracellular matrix protein (ECM) and an increase in portal pressure in the cirrhotic liver. A second component contributing to intrahepatic resistance is that Ang II raises intrahepatic vascular tone and VSMC contraction. As a result, there is an increase in portal pressure through activated HSCs and VSMCs (Figure 1). Activation of the RAAS raises portal pressure,

according to multiple investigations in cirrhotic animals and patients [16].

Olmesartan medoxomil (olmesartan)

Olmesartan (5-methyl-2-oxo-1,3-dioxolen-4-yl) medoxomil (olmesartan) 1-hydroxy-1-methylethyl methoxy-4-A novel AT1 antagonist is CS-866, or 2-propyl-1-{4-[2-(tetrazol-5-yl)-phenyl] phenylmethylimidazol-5-carboxylate. It is a prodrug with an ester moiety that, when taken orally, is quickly cleaved to produce the active form of olmesartan [17].

This medication, which is now marketed for the treatment of hypertension, has a strong and prolonged action and works well when taken once daily. It may also be beneficial for kidney and heart conditions. It works as a blocker of the angiotensin-II receptor to inhibit the renin-angiotensin-aldosterone pathway. It interacts antagonistically with type I and II angiotensin receptors (AT-I and AT-II). This compound selectively and reversibly inhibits AT-I receptors at the adrenal gland and vascular smooth muscle locations, particularly the arterioles, by binding to the AT-I receptor with an affinity greater than 12000 times that of AT-II subtypes. It has been revealed that Olmesartan was superior to the other ARBs examined in lowering diastolic blood pressure in individuals with essential hypertension. Consequently, compared to the other ARBs, this medication might produce better results for portal hypertension and liver fibrosis [16].

Role of Olmesartan in Liver Diseases

According to several recent lines of evidence, the RAAS may significantly influence the pathophysiology of organ fibrosis [16].

Ang II has been demonstrated to stimulate collagen synthesis and proliferation in mesangial cells and other cell types. Furthermore, Ang II increases the expression of transforming growth factor-β (TGF-β) [20].

It has been demonstrated that inhibiting the RAS using AT1 antagonists or angiotensin-converting enzyme (ACE) inhibitors will inhibit organ fibrosis**.** Ang II is thought to control intrahepatic circulation in the liver [16]. According to recent reports, AT1 receptors primarily mediate the proliferation and contraction of human HSCs and the production of TGF-β in rat HSCs induced by Ang II**,** indicating that the advancement of liver fibrosis in vivo is inhibited by ACE inhibitors or AT1 antagonists. According to these results, Ang II and RAS may be crucial in developing liver fibrosis. Moreover, angiogenic chemicals secreted by active HSCs stimulate LSECs, thereby increasing angiogenesis. The significance of angiogenesis in fibrogenesis is demonstrated by the amelioration of liver fibrosis caused by certain angiogenesis-inhibiting medications, such as those that target vascular endothelial growth factor receptor-2 (VEGFR-2)**.** Several studies show that angiotensin II is a powerful vascular smooth muscle cell growth factor that upregulates VEGF and promotes angiogenesis. Furthermore, it has been demonstrated that the AT1R antagonist reduces angiogenesis in hepatocellular carcinoma by inhibiting the VEGF pathway [20].

(3) Somatostatin:

Somatostatin works by attaching itself to the sst1–sst5 family of receptors. Two physiologically active versions of somatostatin are secreted: somatostatin-14, a 14-amino acid peptide, and somatostatin-28, a 28-amino acid peptide. Both forms exhibit high affinity for each of the five receptor subtypes. Octreotide, a commonly used synthetic analog, exclusively binds to sst subtypes 2 and 5 with high affinity and sst3 with reduced affinity [17].

Rat HSC contraction in response to endothelin-1 was somewhat inhibited by activating the somatostatin receptor subtype 1. Both somatostatin and its synthetic analog, octreotide, have favorable safety profiles and are useful in controlling variceal hemorrhage. The half-life of octreotide is longer than that of somatostatin [18].

(4) Statins:

According to previous experimental and human studies, statins (3-hydroxy-3-methyl-COA reductase inhibitors), the most popular lipid-lowering medication, may improve flow-mediated vasodilatation of the liver vasculature in cirrhotic livers and reduce intrahepatic vascular resistance [19].

Statins have pleiotropic effects, such as impacts on fibrogenesis, liver endothelial function and anti-inflammatory and antiangiogenic qualities [21]. They can cause NO upregulation at the liver vasculature by enhancing endothelial NO synthetase activity. Hence, they could be an effective therapy for portal hypertension [20]. Additionally, they have immune-modulating properties and actions that are both antioxidant and antiproliferative [6].

(5) vasopressin and its analogues:

An endogenous peptide hormone called arginine vasopressin causes the mesenteric vascular bed to contract [22]. By binding to vascular vasopressin receptors, vasopressin and its analogs reduce blood flow in the splanchnic circulation, causing the splanchnic arteries to constrict. This effect has been

shown in isolated rats and humans mesenteric arteries. It was abandoned early despite its ability to lower portal pressure since it commonly resulted in cardiovascular problems and water retention. In lowering portal hypertension, terlipressin, also known as triglycyl lysine vasopressin, has recently been proven safer and more effective than vasopressin [23].

(6) Targeting cell death and inflammatory pathways:

Most acute and chronic liver illnesses are accompanied by hepatic inflammation. Improved portal hemodynamics and liver function were linked to the administration of TNF antagonists, such as infliximab. Patients with chronic liver illnesses may benefit from molecules that target inflammation, bacterial translocation, apoptosis or fibrosis (Emricasan, for example) [24].

(7) Antiangiogenesis*:*

Numerous chronic liver illnesses, such as fibrosis, cirrhosis, portal hypertension and hepatocellular carcinoma, are largely influenced by angiogenesis (hepatic angiogenesis is characterized by vascular remodeling that results in capillarization of the sinusoids and the formation of intrahepatic shunts; this process raises vascular resistance and lowers hepatocyte perfusion) [25]. Treatment of portal hypertension and its consequences include antiangiogenic treatment, which specifically targets the production and proliferation of newly created vessels [26]. Vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF) are examples of molecules sensitive to low oxygen levels and are primarily responsible for promoting intrahepatic angiogenesis [27]. Since VEGF is the most effective pro-angiogenic factor, inhibiting the VEGF signal route has often been the main target of anti-angiogenic therapy. Bevacizumab, a humanized monoclonal antibody that neutralizes VEGF, reduces liver failure in vivo by inhibiting the activation of HSCs and neutralizing VEGF produced by hepatocytes [28]. PDGFR and VEGFRs are blocked by several receptor tyrosine kinase inhibitors, including sunitinib and sorafenib, so they lower portal pressure and angiogenesis [29].

(8) Other drugs used in Liver Diseases:

The milk thistle (Silymarin marianum) is the source of the plant flavonoid silymarin, a member of the Benzopyranone class. The compound is actually a triterpene blend of Silibinin, Silydianine, and Silychristine [30].

Role of Silymarin in Liver Diseases

Silymarin has several pharmacological activities, including anti-inflammatory, antifibrotic, antioxidant capabilities and modulation of insulin resistance [30].

A. Antioxidant Properties

Reactive oxygen species (ROS) are produced abnormally when exposed to high concentrations of toxins (such as alcohol and hepatotoxic medications) or when free fatty acid oxidation occurs intensively (i.e., insulin resistance). Endogenous antioxidants may also be depleted due to abnormal production of ROS. By increasing substrate availability (cysteine) for glutathione formation, silymarin increases glutathione production in the liver. This, in turn, improves the antioxidant capacity of liver tissues. Additionally, it guards against harm from a variety of harmful substances, like carbon tetrachloride, by preventing the liver's nuclear factor kappa B (NFκB) activation, which in turn prevents the generation of tumor necrosis factor-alpha (TNF-α), interferon-gamma, interleukin (IL)-2 and IL-4 [31].

(B)Anti-Inflammatory Properties

Even at low concentrations, silymarin inhibited leukotriene B4(LTB4) generation in isolated rat Kupffer cells. The possible anti-inflammatory properties of silymarin may be explained by the specific suppression of LTB4 production by Kupffer cells and potentially other cell types [30].

(C)Antifibrotic Effects

Silymarin has shown antifibrogenic properties in both in vitro and animal models. Silymarin exhibited antifibrogenic effects by dose-dependently preventing growth factor-driven pro-collagen synthesis in human-induced pluripotent stem cells. It has been demonstrated that silymarin greatly inhibited the rise in hepatic collagen type I [32].

(D)Modulation of Insulin Resistance

Insulin resistance is a well-established pathophysiological mechanism in non-alcoholic fatty liver disease, a risk factor for liver cirrhosis. Silymarin improved insulin resistance in a rat model of non-alcoholic fatty liver disease by lowering visceral obesity, stimulating lipolysis and blocking gluconeogenesis [33].

CONCLUSIONS

The main goals of current medications in portal hypertension treatment are to decrease intravascular resistance, which is achieved by blocking hepatic fibrosis and angiogenesis, or to reduce hyperdynamic circulation, vascular hyperplasia, activation of the renin-angiotensin-aldosterone

system and the formation of collateral circulation. As a result of portal hypertension, the neurohumoral (increase in sympathetic activity and activation of the RAAS) and vasoconstrictive systems are activated, leading to increased cardiac output, water and sodium retention and arterial vasodilation in both the splanchnic and systemic circulation. Multiple investigations in cirrhotic animals and humans have shown that RAAS activation raises PP.

No potential conflict of interest was reported by the authors.

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