Infection risk and management strategies for patients with cirrhosis taking proton pump inhibitors

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Purpose: The purpose of this review is to discuss infectious disease–related adverse effects associated with long-term proton pump inhibitor (PPI) therapy in patients with cirrhosis and to provide recommendations for appropriate use and choice of PPI when such therapy is indicated.

Summary: Long-term PPI therapy in patients with cirrhosis increases the risk of infections, with infections in turn increasing the risk of mortality in this patient population. Expert recommendations include restricting long-term PPI use in cirrhosis to patients with appropriate gastrointestinal indications, using a PPI for the shortest possible duration and at the lowest possible dose, and avoiding PPIs with unfavorable pharmacogenetic properties.

Conclusion: Long-term PPI use in patients with cirrhosis has been associated with increased infections. The risk of adverse effects in observational studies, including decompensation, severe infection (especially spontaneous bacterial peritonitis), and increased mortality, appears to increase as the dose and duration of PPI increase.

Keywords: adverse effects, cirrhosis, complications, infectious disease, liver disease, proton pump inhibitors

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Acute-on-chronic liver failure (ACLF) is a syndrome presenting as acute liver deterioration and failure of at least one additional organ in patients with chronic liver disease and cirrhosis. ACLF leads to in-hospital mortality rates at least 5-fold higher than those for admission for cirrhosis without ACLF.[1] In a prospective multicenter investigation of 2 series of patients hospitalized with decompensated cirrhosis and ACLF, the prevalence of infections was 39.7% in one series and 23% in the other. Spontaneous bacterial peritonitis (SBP), urinary tract infections, and pneumonia accounted for the majority of infections, which were frequently due to multidrug-resistant bacteria.[2] The pathogenesis of infections in such patients is complicated by synergistic interactions between internal and external factors. Internal factors include immune and gut dysfunction and reductions in bile flow. External factors include frailty, multiple hospital admissions and antibiotic courses, and long-term use of alcohol and proton pump inhibitors (PPIs).[3] Previous studies have discussed infectious disease–related adverse effects associated with PPI use in patients with cirrhosis. This review aims both to discuss these infectious disease–related adverse effects and to provide practical management strategies for the appropriate use and choice of a PPI when such therapy is indicated.

Data sources

A PubMed search was performed from inception to December 2022 using the terms "proton pump inhibitors" and "cirrhosis" with citations restricted to humans and English language, excluding narrative reviews. Meta-analyses, systematic reviews, clinical reviews, and observational studies were considered for evaluation in this review. This search yielded 436 articles. Articles were excluded if they did not address infectious disease–related

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adverse effects in patients with cirrhosis on PPI therapy. The most recent systematic review or meta-analysis was included when multiple papers covered similar topics. The bibliographies of the included papers were searched for additional relevant papers. No large randomized controlled trials were found that evaluated the adverse effect profile of chronic administration of a PPI vs either placebo or a histamine-2 receptor antagonist (H2RA) in patients with cirrhosis.

KEY POINTS

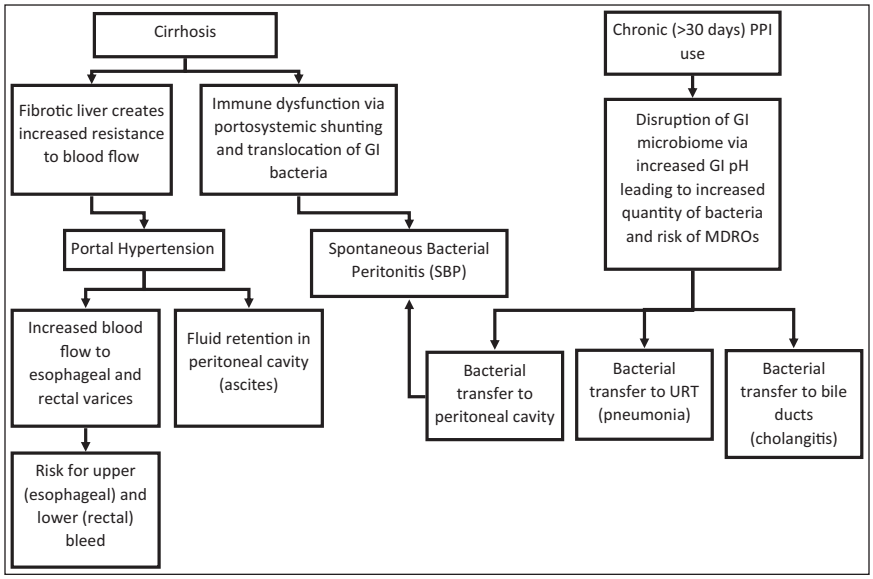
- Patients with cirrhosis on long-term proton pump inhibitor (PPI) therapy are at risk for infectious disease–related complications.
- Recent guidelines provide recommendations for the appropriate use of PPIs.
- Esomeprazole is the preferred PPI in patients with severe liver disease as indicated by Child-Turcotte-Pugh class C cirrhosis.

Cirrhosis with concomitant PPI administration

Immune dysfunction associated with cirrhosis leads to impairment of cellular defenses and serum factors. It can also lead to decreases in phagocytic activity and portosystemic shunting, with decreased clearance of bacteria of gastrointestinal (GI) origin from portal circulation.[4] Additionally, GI tract bacteria are translocated into systemic circulation by mesenteric lymph nodes and the portal vein, predisposing patients to infections such as SBP.[4] Chronic PPI exposure increases the risk for bacterial infections through local effects on GI flora without altering gastric emptying (Figure 1).[5] The association between increases in gastric pH and alterations to gastric flora has been known for decades. For example, in a study published in 1982 by du Moulin et al,[6] 87% of 60 patients receiving antacids or cimetidine had at least one organism cultured simultaneously from the stomach and upper airways. In 33% of these patients, there was a clear sequence of transmission of bacteria from the stomach to the upper airways. While 52% of the patients developed pneumonia, none of these cases occurred in the 8 patients who had mismatching stomach and upper airway flora.[6] In another, more recent study by Schneider et al[7] in patients presenting with acute cholangitis, the use of PPIs was associated with an increase in the number of biliary pathogens (3.14 vs 2.55; $P < 0.01$) and the number of cultures with more than one isolated pathogen (86% vs 76%; $P = 0.04$). Recent evidence demonstrates that disruption of the intestinal microbiome by medications such as PPIs not only increases the quantity of bacteria but also results in increased odds of culturing multidrug-resistant organisms such as the order Enterobacterales and vancomycin-resistant enterococci (odds ratio [OR], 1.74; 95% confidence interval [CI], 1.40-2.16).[8] In addition to increasing the risk of infections, PPIs could have adverse effects on a wide range of organ systems by impairing proton pump activity in endothelial lysosomes apart from those in the GI tract, leading to disruption of proteostasis and accelerated senescence.[9]

The first (published in 2019) and largest randomized double-blind trial evaluating long-term (median evaluation of 3 years) safety concerns with

Figure 1. Cirrhosis pathophysiology and proton pump inhibitor contribution to spontaneous bacterial peritonitis.[4-8] GI indicates gastrointestinal; MDROs, multidrug-resistant organisms; PPI, proton pump inhibitor; SBP, spontaneous bacterial peritonitis; URT, upper respiratory tract.



PPIs found no risk beyond that of enteric infections; however, the trial was not limited to patients with chronic liver disease.[10] In the COMPASS trial, 17,598 participants with cardiovascular disease and peripheral artery disease, including 168 with liver disease, were randomly assigned using a factorial design to receive pantoprazole 40 mg daily or placebo with additional assignment to rivaroxaban or aspirin. The trial involved data collection for a variety of infectious (eg, *Clostridioides difficile*, enteric infections, pneumonia) and noninfectious (eg, chronic kidney disease, diabetes, lung disease, cardiovascular disease, cancer) complications in addition to hospitalizations and mortality. The only statistically significant difference found in patients receiving PPI therapy was an increase in the rate of enteric infections (OR, 1.33; 95% CI, 1.01-1.75), with more numeric cases of *C. difficile* based on only 13 events.[10]

Given the limited data available from randomized trials, cohort and case-control studies are the most common methodologies serving as the basis for the increases in morbidity and mortality noted with chronic PPI exposure, particularly for patients with cirrhosis. For example, in a longitudinal observational study conducted by the Department of Veterans Affairs (VA) in which the median duration of patient follow-up was over 5 years, there was an increased rate of death with a PPI compared to no PPI (hazard ratio [HR], 1.15; 95% CI, 1.14-1.15) or an H2RA (HR, 1.25; 95% CI, 1.23-1.28), with a graded association noted between duration of therapy and death in new PPI users.[11] In a similar study conducted by the VA in patients with cirrhosis, use of PPIs was associated with more severe infection (HR, 1.21; 95% CI, 1.18-1.24) and decompensation (HR, 1.64; 95% CI, 1.61-1.68).[12] SBP was the infection type with the strongest association of risk with PPI use (HR, 1.77; 95% CI, 1.66-1.88; $P < 0.001$). However, the cause-specific increase in mortality associated with PPI therapy was limited to patients with liver-related mortality (HR, 1.23; 95% CI, 1.19-.128). There was a reduction in non–liver-related mortality with PPI therapy (HR, 0.88; 95% CI, 0.85-1.91) and in all-cause mortality in patients with hospitalization for GI bleeding (HR, 0.88; 95% CI, 0.84-0.91).[12]

The findings of published systematic reviews are consistent in demonstrating an increase in morbidity and mortality associated with chronic PPI exposure in patients with cirrhosis and chronic liver disease. For example, in a systematic review of 35 cohort studies and 12 case-control studies published by Wang et al[13] in 2020, chronic PPI use in patients with chronic liver disease led to an increase in the odds of hepatic encephalopathy (OR, 2.31; 95% CI, 1.63-3.28), SBP (OR, 1.72; 95% CI, 1.42-2.09), bacterial infections (OR, 1.76; 95% CI, 1.52-2.03), and overall mortality (OR, 1.29; 95% CI, 1.11-1.49), albeit with substantial heterogeneity noted in the last finding (I^2 = 75%).[13] Of the 25 studies included in the SBP analysis, 9 were performed in patients with ascites. In this analysis, PPI use was associated with a significant increase in the incidence of SBP in patients with cirrhosis and ascites compared to patients without ascites (OR, 1.18; 95% CI, 1.04-1.34).[13]

Similar negative outcomes associated with chronic PPI exposure in patients with cirrhosis have been reported in other recent systematic reviews, including in those evaluating specific infectious disease–related complications, particularly SBP.[14-20] Three studies that examined chronic PPI use in cirrhosis found increased incidence of SBP and overall infections.[14-16] A systematic review and meta-analysis by Hwang et al[14] published in 2022 that examined 29 studies found an increased risk of SBP in 23 studies (relative risk, 1.31; 95% CI, 1.10-1.55; I^2 = 73.0%), while a 2015 review of 12 studies described similar results (increased risk of SBP with PPI use; OR, 2.17; 95% CI, 1.36-2.87; I^2 = 0%).[15] A 2016 meta-analysis of 16 studies by Yu et al[16] described increased SBP risk with PPI use (OR, 2.11; 95% CI, 1.46-3.06; I^2 = 85%) but excluded patients who experienced a GI bleed in the 2 weeks before SBP incidence.

The degree of acid suppression imparted by PPIs may play a role in the observed increases in infection risk. Two studies compared the use of PPIs and H2RAs while examining their impact on SBP incidence and infection rates in cirrhosis. Both studies found that PPIs had a greater impact on SBP incidence than H2RAs. In a 2013 meta-analysis by Deshpande et al,[19] PPI use significantly increased the risk of SBP in hospitalized patients with cirrhosis (OR, 3.15; 95% CI, 2.09-4.74; I^2 = 57%), while H2RA use increased risk but the difference did not reach statistical significance.[19] Statistical significance was demonstrated with both PPI and H2RA use in a 2015 systematic review and meta-analysis by Khan et al.[20] In this review of 14 observational studies, SBP incidence was increased with both acid-suppressing medication classes, with PPIs having a stronger impact (PPI use: OR, 2.32; 95% CI, 1.57-3.42; I^2 = 82%; H2RA use: OR, 1.93; 95% CI, 1.15-3.24; I^2 = 0%).[20]

Adverse effect concerns related to PPIs extend to patients receiving them as well as the clinicians who commonly prescribe them. In one national survey of patients receiving PPIs for gastroesophageal reflux disease (GERD), 46% of respondents were aware of at least one PPI-related adverse effect.[21] Of the 39% of patients attempting to stop PPI therapy, only 17% were doing so based on prescriber recommendations.[21] In a survey of 799 internists, 70% were somewhat or very concerned about PPI adverse effects and 76% had somewhat or very much changed their prescribing based on these concerns.[22] Such concerns about adverse effects have led to a more limited set of indications for what experts believe are appropriate evidence-based uses of PPI therapy. For example, in a publication from 2008, appropriate PPI indications "strongly supported by the medical literature" for patients with cirrhosis included the generic categories of peptic ulcers, GERD, nonsteroidal anti-inflammatory drug (NSAID) symptoms or ulcer prevention, and previous GI bleeding.[23]

In contrast, a clinical practice update by the American Gastroenterological Association has categories for long-term (>8 weeks) and short-term (≤8 weeks) PPI therapy, with additional subcategorization as definitely, conditionally, or not indicated.[24] Seven conditions were listed as definitive indications for long-term PPI therapy: Barrett's esophagus, grade C/D erosive esophagitis, esophageal strictures from GERD, Zollinger-Ellison syndrome, eosinophilic esophagitis, high risk for aspirin/NSAID-related bleeding, and prevention of progression of idiopathic pulmonary fibrosis. Even these allowable indications had additional caveats. The guidelines noted that, while most PPIs are prescribed by primary care physicians, additional review (particularly in healthcare settings) by a pharmacist or nurse specialist is recommended as part of a multidisciplinary approach to identify inappropriate PPI use for possible discontinuation.[24]

Three PPIs are available in the US without a provider-written prescription or consultation with a medical professional. Lansoprazole, omeprazole, and esomeprazole are approved as nonprescription therapy for short-term (2 weeks or less) management of frequent heartburn (2 or more days per week).[25-27] This shortened duration of use is considered to confer a low risk of adverse drug effects and long-term complications.[28] The risk to users, including those with cirrhosis, is increased when these medications are taken for longer durations by patients practicing self-care. This has been noted as a potential confounder when estimating population use of PPIs.[29,30] Patients may not be aware of or concerned about long-term nonprescription use of PPIs, as they are often packaged for sale in quantities that exceed the 2-week short-term limit.[25-27]

A prospective, multicenter, randomized, double-blind, placebo-controlled, parallel-group trial has been planned to evaluate the effects of PPI withdrawal in patients with complicated cirrhosis, which should help to answer questions more specific to this patient population.[31] The trial, known by the acronym STOPPIT, will include patients receiving PPI therapy for more than 28 days who have been hospitalized within the previous 42 days due to a complication of cirrhosis. Exclusion criteria include recent high-grade reflux esophagitis, peptic ulcer disease, endoscopic therapy for esophageal varices, and daily use of NSAIDs. Patients will be randomized to receive esomeprazole 20 mg or placebo for 360 days with a primary composite endpoint of time to rehospitalization and/or death. There are also plans to evaluate intestinal microbiota, as well as a variety of safety endpoints.[31]

Recommendations by expert panels

Despite the lack of high-level evidence–based data upon which to base recommendations for the choice of PPI in patients with cirrhosis, information is available to help guide clinical decision-making. One such source is guidance on PPIs that was implemented in 2 national drug databases in the Netherlands in 2017.[32] The information was derived from registration authorities, literature, and expert opinion using a 6-step process of (1) evidence collection, (2) data extraction and presentation, (3) initial safety classification and dose suggestions for PPIs, (4) discussion and conclusions by an expert panel, (5) implementation, and (6) continuity of the process with ongoing literature evaluation and discussions by the expert panel. The expert panel comprised gastroenterologists, a general practitioner, and hospital and community pharmacists who review the lead pharmacist's suggestions. Both pharmacokinetic and safety data were evaluated for this review. High PPI exposure with long-term therapy was considered to be the major safety risk. The recommendations from the 2017 compilation are that esomeprazole, omeprazole (20 mg/day maximum), and rabeprazole (10 mg/day maximum) be the PPIs of choice in patients with Child-Turcotte-Pugh (CTP) class A or B cirrhosis. Only esomeprazole (20 mg/day maximum) is recommended in patients with CTP class C cirrhosis. Both pantoprazole and lansoprazole are considered to be unsafe because of a 4- to 8-fold increase in exposure in patients with cirrhosis due to a low hepatic extraction ratio with clearance dependent on CYP2C19 function and protein binding. Safety concerns from observed adverse effects for lansoprazole were limited to case reports, while pantoprazole was considered to be well tolerated. Thus, the recommendation to avoid lansoprazole and pantoprazole is due to the marked pharmacokinetic alterations in patients with cirrhosis and the availability of other agents that lack these properties. In contrast, esomeprazole is least affected by changes in CYP2C19 activity and is well tolerated in patients with cirrhosis.[32]

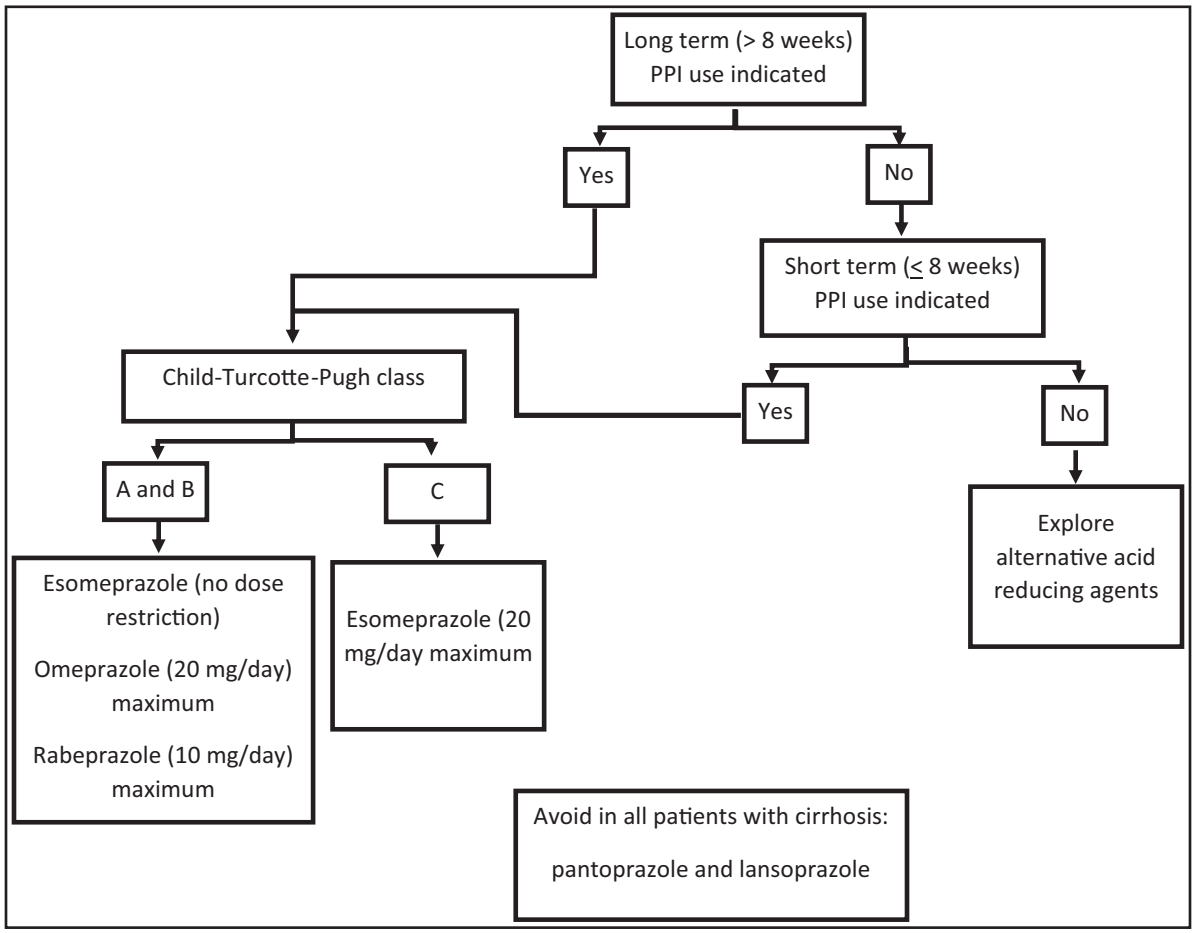
The recommendations for PPI use in patients with cirrhosis by another panel of 10 experts following a systematic literature search are generally consistent with those from the Netherlands group, with pantoprazole and lansoprazole considered to be unsafe.[33] Use of omeprazole and rabeprazole is considered safe for CTP class A or B cirrhosis, with appropriate dose adjustment of esomeprazole considered to be safe with no additional risks, while dosage adjustment is needed with more severe disease.[33]

The Food and Drug Administration (FDA) recommends considering dose adjustments for lansoprazole in patients with severe hepatic disease but does not provide specific dose recommendations.[34] In contrast, FDA does not require dose adjustments for pantoprazole in severe hepatic disease but states that doses over 40 mg per day have not been studied in this population.[35]

Figure 2 provides a decision tree for PPI use in cirrhosis that summarizes the more important considerations discussed in this paper.

The recommendations from the expert panel in the Netherlands are useful, but, like recommendations

Figure 2. Decision tree for proton pump inhibitor (PPI) use in cirrhosis.[23,24,32,33]



developed by panels for clinical practice guidelines, they often do not address patient-specific considerations (ie, personalized medicine). For example, PPIs are prodrugs that undergo rapid hepatic metabolism primarily by CYP2C19 and CYP3A4. In patients with impaired liver function due to cirrhosis, the area under the curve (AUC) can increase 7-fold.[36] These metabolism-related concerns are further exacerbated by potential drug-drug interactions, as exemplified by the combination of PPIs and clopidogrel. The product information for esomeprazole states that concomitant use of clopidogrel should be avoided because of esomeprazole's inhibition of CYP2C19, which impairs the metabolism of clopidogrel to its active metabolite.[37] In contrast, rabeprazole is primarily metabolized by CYP3A4, resulting in a reduction in the mean AUC of clopidogrel's active metabolite of approximately 12%, with no statement about avoiding concomitant use of the 2 drugs in rabeprazole's product information.[38] The product information for clopidogrel does not mention rabeprazole but has a figure showing the change in exposure with concomitant administration of dexlansoprazole (weakest interaction), lansoprazole, pantoprazole, and omeprazole (strongest interaction).[39]

Another patient-specific consideration, although not specific to patients with cirrhosis, is rebound gastric acid hypersecretion, which may make the process of discontinuing PPIs more difficult for both patients and providers. Rebound gastric acid hypersecretion is the phenomenon of increased gastric reflux that occurs when acid-suppressing medications are discontinued or quickly tapered. The exact mechanism behind rebound gastric acid hypersecretion is unclear but has been theorized to be a consequence of chronic gastric pH elevation causing an increase in gastrin, leading to hyperplasia of enterochromaffin-like cells and finally increased gastric acid and rebound of symptoms.[40,41] To address rebound gastric acid hypersecretion, some experts recommend tapering PPIs when discontinuing therapy. Guidelines or data supporting a specific tapering method are lacking, but decreasing the total PPI dose by 50% every 1 to 2 weeks has been evaluated in clinical trials.[42,43]

Summary

ACLF is associated with at least 5-fold–increased mortality in patients with cirrhosis. A prospective multicenter trial found that infections were present in approximately

one-third of patients hospitalized with ACLF.[1,2] Considering the mortality risk, it is imperative to identify risk factors for, and steps to prevent, infections in this patient population. Long-term PPI use in patients with cirrhosis has been associated with increased incidence of infections.[14-20] The risk of adverse drug events in observational studies, including decompensation, severe infection (especially SBP), and increased mortality, appears to increase as the dose and duration of the PPI increase.[11,12] These same studies found a mortality benefit when PPIs were employed as a treatment for GI bleed. On the basis of concerns for adverse drug events, guidelines support the long-term use of PPIs only for appropriate indications and with agents that have the lowest risk in this population. Preferred agents include esomeprazole, omeprazole, and rabeprazole in patients with CTP class A or B cirrhosis and only esomeprazole in patients with CTP class C cirrhosis. With a lack of data available from randomized controlled trials, expert recommendations are used to inform clinical decision-making.

Data availability

No new data were generated or analyzed in support of this article.

Disclosures

The authors have declared no potential conflicts of interest.

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