Cirrhotic Complications & Considerations: A Focus on Management Strategies

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Goals and Objectives

At the end of this presentationPHARMACISTS should be able to:
1. Identify risk factors for developing cirrhosis
2. Recognize common laboratory findings and clinical presentations associated with cirrhotic complications
3. Identify medications to more closely monitor and potentially discontinue in patients with cirrhosis
4. Recommend appropriate strategies for the prevention and treatment of variceal bleeds
5. Create individualized regimens for patients with hepatic encephalopathy

Goals and Objectives

At the end of this presentationPHARMACY TECHNICIANS should be able to:
1. Understand the pathophysiology for the progression to cirrhosis
2. List the different tools used to diagnose a patient with cirrhosis
3. Recognize four complications related to cirrhosis
4. Identify medications used in the management of hepatic encephalopathy

Cirrhosis Statistics

• 36,427 deaths in 2013 & 31,802 deaths in 2010
• 101,000 hospital discharges with chronic liver disease
• Ranked as 12th leading cause of death in the United States

Liver

• Elaborate blood filtration system
• Detoxification and metabolism
• Production of proteins

Liver Disease

• Greatest regenerative capacity of any organ in the body
  • Due to the highly vascular nature
  • Regenerates mass after partial hepatectomy
  • Repetitive long-term damage → fibrosis
Cirrhosis

- Late stage of progressive hepatic fibrosis
- Remodeling of hepatic architecture and formation of regenerative nodules
- Reversal has been documented in several forms of disease
- Irreversible in advanced stages
  - Liver transplantation

### Etiology of Cirrhosis

<table>
<thead>
<tr>
<th>Etiology of Cirrhosis</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcoholic liver disease</td>
<td>60 to 70</td>
</tr>
<tr>
<td>Chronic hepatitis (B or C)</td>
<td>10</td>
</tr>
<tr>
<td>Non-alcoholic fatty liver disease</td>
<td>10</td>
</tr>
<tr>
<td>Biliary obstruction</td>
<td>5 to 10</td>
</tr>
<tr>
<td>Hemochromatosis</td>
<td>5 to 10</td>
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</table>

### Risk Factors

- Long-term excessive alcohol use
- Unprotected sexual intercourse
- Intravenous (IV) drug use
- Non-sterilized tattoos and piercing
- Medications
- Obesity
- Smoking

### Classification of Cirrhosis

- **Compensated cirrhosis:** No symptoms associated with cirrhosis
- ** Decompensated cirrhosis:** Clinically evident complications related to cirrhosis

### Clinical Presentation

<table>
<thead>
<tr>
<th>Non-Specific Symptoms</th>
<th>S/S of Hepatic Decompensation</th>
<th>Physical Exam</th>
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</thead>
<tbody>
<tr>
<td>Weight loss/Anemia</td>
<td>Hepatomegaly</td>
<td>Digital clubbing</td>
</tr>
<tr>
<td>Weakness</td>
<td>Circulatory changes</td>
<td>Jaundice</td>
</tr>
<tr>
<td>Fatigue</td>
<td>Endocrine changes</td>
<td>Dupuytren's contracture</td>
</tr>
<tr>
<td>Cramps</td>
<td>Bleeding</td>
<td>Splenomegaly</td>
</tr>
<tr>
<td>Nausea</td>
<td>Abdominal distension</td>
<td>Vascular spiders</td>
</tr>
<tr>
<td>Osteoporosis</td>
<td>Confusion</td>
<td>Palmar erythema</td>
</tr>
</tbody>
</table>


Laboratory Findings in Cirrhosis

<table>
<thead>
<tr>
<th>Impaired Hepatocyte Function</th>
<th></th>
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<tbody>
<tr>
<td>Elevated bilirubin</td>
<td></td>
</tr>
<tr>
<td>Elevated alanine transaminase (ALT), aspartate transaminase (AST)</td>
<td></td>
</tr>
<tr>
<td>Cholestatic</td>
<td></td>
</tr>
<tr>
<td>Elevated gamma-glutamyl transpeptidase (GGT)</td>
<td></td>
</tr>
<tr>
<td>Elevated alkaline phosphatase (ALP)</td>
<td></td>
</tr>
<tr>
<td>Impaired Synthetic Function</td>
<td></td>
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<tr>
<td>Elevated prothrombin time (PT)</td>
<td></td>
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<tr>
<td>Elevated international normalized ratio (INR)</td>
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</tbody>
</table>

Hypoalbuminemia
Thrombocytopenia

Diagnosis

- Ultrasonography
  - Routinely used
  - Sensitive and specific
- Computed tomography (CT) and magnetic resonance imaging (MRI)
  - Expensive
- Liver biopsy
  - Gold standard for definitive diagnosis
  - Not always necessary
- Clinical markers
  - Liver function tests (LFTs), INR, albumin, etc.

Prognostic Scores

- Model for End-Stage Liver Disease (MELD) Score
  - Predicts 3 month mortality
  - Based on serum creatinine, INR, total bilirubin
  - Higher score = more severe
- Child-Pugh Score
  - Predicts survival at 1 and 2 years post-diagnosis
  - Based on total bilirubin, serum albumin, PT, ascites, hepatic encephalopathy
  - Classification
    - A (5-6 points) = less severe
    - B (7-9 points) = intermediate
    - C (10-15 points) = more severe

Liver Transplant

- Life-saving treatment
  - Hepatitis C is most common reason for transplant in U.S.
  - Cirrhosis due to long-term alcohol use is second
- Thorough evaluation of candidates by transplant team
- Liver transplant selection committee review
  - National waiting list maintained by United Network for Organ Sharing (UNOS)
  - Use of MELD to shorten list and waiting time
  - 80-85% functioning after 1 year
  - UIHC closest transplant center
  - 14,792 U.S. liver transplant waiting list as of 01/2016
  - 6,483 donors in 2015

Goals of Therapy

- Prevent and prolong time to liver transplant
- Avoid potential complications:
  - Portal hypertension
  - Ascites
  - Infection
  - Variceal bleeds
  - Hepatic encephalopathy
  - Others:
    - Hepatorenal syndrome
    - Hepatopulmonary dysfunction
    - Endocrine dysfunction

Portal Hypertension

- Product of elevated hepatic resistance + increased portal inflow
- Result of structural and hormonal changes
- Vasoactive hormones
  - Nitric oxide (NO)
  - Renin-angiotensin-aldosterone system (RAAS)
  - Antidiuretic hormone (ADH)
  - Present in 80-90% of asymptomatic patients with cirrhosis
**Portal Hypertension**

- Clinical manifestations
  - Splenomegaly
  - Thrombocytopenia
- Diagnosis
  - Known risk factor (i.e. cirrhosis) plus clinical manifestation
  - Can measure hepatic venous pressure gradient (HVPG)
- Treatment
  - Transjugular intrahepatic portosystemic shunt (TIPS)
  - Goal to treat and prevent associated complications

**Ascites**

- Most common major complication of cirrhosis
  - Also, most common complication that leads to hospitalization
  - Accumulation of excessive fluid within peritoneal cavity
  - Portal hypertension (+) renal water and sodium retention → leakage of fluid into peritoneal cavity

**Ascites Management**

1. Diuretics
2. Sodium restriction
   - Recommended restriction to 2000 mg per day
3. Alcohol cessation
   - May reduce or normalize portal pressure
   - Better response to diuretic therapy
4. Evaluate for medications that may worsen condition
   - ACE inhibitors/ARBs
   - NSAIDs
5. Infection identification and management
6. Paracentesis

**Diuretics**

- Initial therapy: Loop diuretic + aldosterone antagonist

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**Cirrhosis**

- Distorted hepatic architecture
- Elevated hepatic resistance
- Vasoactive hormones causing dilation
**Diuretics**

- Spironolactone 100 mg and furosemide 40 mg daily
- Titrate every 3-5 days as tolerated
- Max spironolactone 400 mg and furosemide 160 mg daily
- Benefits: normokalemia, better urine sodium excretion, faster mobilization
- Lower doses for elderly patients or weight < 50 kg
- Alternative: spironolactone monotherapy
- Spironolactone effect > furosemide
- IV furosemide should be avoided

**Benefits:**
- Normokalemia
- Better urine sodium excretion
- Faster mobilization

**Lower doses:**
- For elderly patients or weight < 50 kg

**Alternative:**
- Spironolactone monotherapy
- Spironolactone effect > furosemide
- IV furosemide should be avoided

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**Monitoring**

- Daily weights
- Electrolytes, kidney function, orthostatic symptoms
- Ascites resolution
- Gynecomastia
  - Alternative: amiloride 10-40 mg/day or eplerenone 25 mg/day
- Discontinuation of diuretics
  - Hepatic encephalopathy development
  - Hyponatremia
  - Serum creatinine > 2.0 mg/dL
  - Reversible cause of ascites is found

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**Refractory Ascites**

- 10% of patients with ascites and cirrhosis
- Poor prognosis
- Decreases survival from 50% at two years to 50% at 6 months
- Referral for liver transplantation
- Classified by one of the following criteria:
  - Inability to mobilize ascites
  - Rapid re-accumulation of fluid after therapeutic paracentesis
  - Development of diuretic related complications

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**Refractory Ascites Management**

- **Stop anti-hypertensives**
- **Avoid NSAIDs**
- Midodrine 5 mg by mouth three times daily
- Titrate by 2.5 mg to max dose of 17.5 mg three times daily
- Increases systolic blood pressure 10 to 15 mmHg
- **Invasive measures**
  - Serial large-volume paracentesis (> 5 L removed) every 2 weeks with replacement albumin 6-8 g/L removed
  - **TIPS placement**

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**Ascites Summary**

- Most common complication of cirrhosis
- Ratio of furosemide 40 mg daily: spironolactone 100 mg daily initial treatment of choice
- Alcohol abstinence and sodium restriction (2000 mg/day) are crucial to success
- Referral for liver transplantation in refractory ascites
- Evidence for midodrine use in refractory ascites
- Albumin replacement of 6-8 g/L removed with large volume paracentesis
Spontaneous Bacterial Peritonitis (SBP)

- Present in 10-25% of patients with ascites
- Abdominal pain, fever, confusion, nausea, vomiting
- Start empiric treatment if cirrhosis and ascites with signs or symptoms of infection + unclear source
- Diagnosis
  - Positive ascitic fluid bacterial culture (E. coli, K. pneumoniae)
  - Ascitic fluid polymorphonuclear count (PMN) ≥ 250 cells/mm³
- IV therapy with 3rd generation cephalosporin x 5 days
  - Cefotaxime 2g IV every 8 or ceftriaxone 1g IV every 24 hrs
- Co-treatment with IV albumin 1.5 g/kg on day 1 and 1 g/kg on day 3

Runyon B. Hepatology. 2009; 49(6) 2087-2107.
Runyon B. Gastroenterol. 1991; 100(6):1737.

Gastroesophageal Varices

- Identify present varices and prevent hemorrhage
- 25 - 40% of patients with cirrhosis and 30% mortality per occurrence
- Risk of hemorrhage can be predicted by: location, size, appearance and pressure of the varices
- HVPG > 12 mmHg
- Esophagogastroduodenoscopy (EGD): Diagnostic tool


Primary Prophylaxis

- Non-selective beta-blockers (NSBB) used to prevent hemorrhage in patients with varices
- Portal hypertension → increased cardiac output (CO) and increased splanchnic blood flow → portosystemic shunts
- NSBB decreases CO via β-1 and induces splanchnic vasoconstriction via β-2 receptors
  - Decreases portal inflow
  - Decreases variceal flow
- Selective beta-blockers are not as effective in reducing portal venous pressure


Primary Prophylaxis

<table>
<thead>
<tr>
<th>Variceal Size</th>
<th>Bleed Risk</th>
<th>Recommended Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>No increased bleed risk</td>
<td>NO NSBB; surveillance endoscopies</td>
</tr>
<tr>
<td>Small (&lt; 5 mm)</td>
<td>No increased bleed risk</td>
<td>+/- NSBB</td>
</tr>
<tr>
<td>Small (&lt; 5 mm)</td>
<td>Increased bleed risk</td>
<td>NSBB</td>
</tr>
<tr>
<td>Medium - Large (6-8 mm)</td>
<td>Increased bleed risk</td>
<td>NSBB or Endoscopic variceal ligation (EVL)</td>
</tr>
<tr>
<td>Medium - Large (6-8 mm)</td>
<td>No increased bleed risk</td>
<td>NSBB</td>
</tr>
</tbody>
</table>

* Increased bleed risk = Child B/C or presence of red wale marks on varices
Primary Prophylaxis: NSBB

- Propranolol 20 mg twice daily
- Nadolol 40 mg daily
- Carvedilol 6.25 mg twice daily
- Decrease in portal-collateral blood flow & decrease in hepatic vascular resistance
- Shown to reduce HVPG more than propranolol
- Monitoring: Heart rate, kidney function, blood pressure
- Safety: Reduction in cardiac output and splanchnic blood flow may be harmful in decompensated cirrhosis

References:

Beta-Blocker “Window”

Early cirrhosis
- Beta-blockers are not indicated in early cirrhosis, may increase adverse
- Beta-blockers may be indicated for cardiovascular indications

Window opens
- Beta-blockers are indicated for primary prophylaxis of variceal bleeding
- Beta-blockers may be indicated for secondary prophylaxis of variceal bleeding

Window closes
- Beta-blockers are contraindicated under the following situations
  - Palpable ascites
  - Systolic blood pressure < 90 mmHg
  - Mean arterial pressure < 60 mmHg
  - Acute kidney injury
  - Hepatorenal syndrome
  - Spontaneous bacterial peritonitis
  - Episodic
  - Poor medical follow-up
  - Patient noncompliance

Pharmacological Therapy

- Vasopressin +/- nitrate: potent splanchnic vasoconstrictor
  - Continuous IV infusion 0.2-0.4 units/min; max 0.8 units/min x 24 hours
  - With IV nitroglycerin 40 mcg/min; max 400 mcg/min to systolic pressure > 90 mmHg

- Octreotide: local vasoconstrictive effect
  - IV bolus 50 mcg followed by continuous infusion of 50 mcg/hr
  - Associated with tachyphylaxis - adjunct to endoscopic therapy
  - Administered between 2-5 days
  - Recent RCT: 2 days of therapy is as effective as 5 days

References:

Varices Summary

- Primary prophylaxis with NSBB for cirrhotic patients without varices is not recommended
- Active surveillance every 2-3 years with endoscopy
- Switch from selective beta-blocker to NSBB for the prevention of variceal hemorrhage with varices present
- NSBBs may do more harm in late stages of cirrhosis
- Octreotide is preferred agent for acute bleeds
  - Recent study shows 2 day treatment adequate

References:
- Runyon BA. Hepatology 2013;57:1651.

Infection Prophylaxis

- Cirrhosis and gastrointestinal bleeding
  - Short-term prophylactic antibiotics
  - 7 day course
  - Ceftriaxone 1 gram IV daily
  - Trimethoprim 160 mg/sulfamethoxazole 800 mg one double-strength tablet once daily
  - Preferred
  - Ciprofloxacin 500 mg tablet once daily
  - Alternative

References:
Infection Prophylaxis

- History of SBP
- Cirrhosis and ascites consider long-term antibiotic prophylaxis:
  - Ascitic protein concentration < 1.5 g/dL AND
  - Impaired renal function (Scr > 1.2, BUN > 25, or serum sodium < 130) OR liver failure (Child score > 9 and bilirubin > 3)
- Trimethoprim 160 mg/sulfamethoxazole 800 mg once daily
  - Preferred
- Ciprofloxacin 500 mg once daily
  - Alternative

Quick Quiz

74 year old female with PMH of cirrhosis admitted with severe vomiting of bright red blood along and worsening fatigue and weakness.
Hgb 7.7 g/dL, BP 77/49 mmHg
EGD reveals esophageal variceal hemorrhage
Select the appropriate initial therapies:

a) Start ceftriaxone 1 gm IV Q24h + octreotide 50 mcg bolus followed by 50 mcg continuous infusion
b) Start Bactrim 160 mg/800 mg tablet once daily + propranolol + vasopressin +/- nitrate
c) Start vancomycin and piperacillin-tazobactam STAT
d) No antibiotics are indicated at this time + octreotide 50 mcg bolus followed by 50 mcg continuous infusion

Hepatic Encephalopathy (HE)

- HE is a neuropsychiatric syndrome
- Debilitating, may occur without warning
- Pathogenesis is not well understood
  - Possibly related to increase in ammonia concentration
- Clinical diagnosis based on two concurrent types of symptoms
  - Impaired mental status
  - Impaired neuromotor function

HE Management

- Supportive care
  - Nutrition and prevention of dehydration
  - Fall precautions
- Acute care
  - Correct precipitating cause if possible
  - Therapy to lower ammonia concentrations
- Chronic care
  - Management of recurrent HE or HE that impairs quality of life

HE Acute Management

- Correct precipitating cause(s)
  - Renal failure, hypokalemia, constipation, infection, hypovolemia, GI bleed
- Lower ammonia concentrations
  - Ammonia levels alone do not add any diagnostic, staging, or prognostic value
HE Acute Management

- Lactulose 30-45 mL (20-30 grams) given 2-4 times/day
  - Oral solution, titrated to achieve 2-3 soft stools per day
  - Degradation causes conversion of ammonia to ammonium and enhances diffusion of ammonia into the gut
  - ADE: sweet taste, GI side effects (bloating, flatulence, severe unpredictable diarrhea)
  - Monitor: electrolytes, diarrhea, ammonia levels

- Lack of improvement after 48 hours → addition of Rifaximin 400 mg orally every 8 hours
  - Antibiotic with poor oral bioavailability
  - Suppresses intestinal flora to reduce bacterial production of ammonia
  - Alternatives: neomycin, vancomycin, metronidazole
  - Ototoxicity, nephrotoxicity, and peripheral neuropathy limit use

Evidence for Rifaximin

<table>
<thead>
<tr>
<th>Study Design</th>
<th>Randomized, double-blind, placebo-controlled trial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population</td>
<td>299 patients with history of recurrent HE from chronic liver disease</td>
</tr>
<tr>
<td>Intervention(s)</td>
<td>Rifaximin 550 mg twice daily vs. placebo over 6 months</td>
</tr>
<tr>
<td>End Point</td>
<td>Primary: time to first breakthrough episode of HE Secondary: time to first hospitalization for HE</td>
</tr>
</tbody>
</table>

| Results |
|---------|------------------|
| Relative reduction in risk of breakthrough episode with rifaximin by 58% vs. placebo HR 0.42 (95% CI, 0.28-0.64; P<0.001) |
| Relative reduction in risk of hospitalization with rifaximin by 50% vs. placebo HR 0.50 (95% CI, 0.29-0.87; p=0.01) |

- >90% of patients received concomitant lactulose therapy
- Incidence of adverse effects was similar between groups

Zinc for HE

- Zinc deficiency common in cirrhosis
  - 96% prevalence for MELD score 12
- Ammonia-reduction pathways impaired by deficiency
- Treatment with zinc found to enhance formation of urea from ammonia
  - Well-tolerated with rare adverse effects long-term
  - Dysepsia and copper deficiency
  - Lack of data to support optimal dose

Rifaximin vs. Lactulose/Lactitol

<table>
<thead>
<tr>
<th>Study Design</th>
<th>Meta-analysis of 8 randomized-controlled trials</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population</td>
<td>Adults with signs or symptoms of acute, chronic HE</td>
</tr>
<tr>
<td>Intervention(s)</td>
<td>Rifaximin 1200 mg/day vs. lactulose 45-120 mL/day</td>
</tr>
<tr>
<td>Outcomes</td>
<td>Primary: Improvement of HE clinical syndrome</td>
</tr>
</tbody>
</table>

| Results |
|---------|------------------|
| No difference in efficacy found between rifaximin and lactulose (RR 1.06, 95% CI 0.94-1.18, P=0.34) |
| Rifaximin → less risk of diarrhea (RR 0.11, 95% CI 0.04-0.31; P=0.0001) and lower rate of abdominal pain (RR 0.19, 95% CI 0.10-0.37; P=0.0001) |
| No difference in improvement of mental status (P=0.07) and grade of asterixis (P=0.23) |

<table>
<thead>
<tr>
<th>Conclusion</th>
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<tr>
<td>Considering small sample size &amp; expense, patients with severe ADE to lactulose could use rifaximin instead</td>
</tr>
</tbody>
</table>

HE Chronic Management

- Generally treatment continued indefinitely if successful acutely
  - Exception: known precipitating factor is controlled
- Best evidence for lactulose 20-30 grams three times daily as maintenance therapy
  - Adherence is key
- Recurrent HE on chronic lactulose
  - Addition of rifaximin 550 mg twice daily recommended
  - Refractory HE on lactulose and rifaximin
  - Evaluation for portosystemic (PS) shunt
  - Addition of zinc
  - Addition of branched-chain amino acids (BCAA)

Evidence for Polyethylene glycol (PEG)

- Randomized to receive 4 liters of PEG or lactulose 20-30 g x 3 over 24 hours
- PEG showed more improvement in HE scoring algorithm vs. lactulose
Zinc for HE

- RCT 2010: 79 patients HE grades 1 & 2
  - Polaprezinc 225 mg + lactulose + BCAA vs. lactulose + BCAA followed for 6 months
  - Polaprezinc only available in Japan
- Zinc arm improved HE grade, blood ammonia levels, Child-Pugh score, and neuropsychological tests (P=0.03, P=0.04, P=0.02 respectively)
- Associated with improvement in physical component scale (P=0.03), but not mental component scale (P=0.98)
- Conclusion: zinc supplementation is effective in HE and improves health related quality of life

HE Management Summary

- Supportive care
  - Nutrition, hydration, fall precautions
- Acute care
  - Correct precipitating cause if possible
    - GI bleed, infection, hypovolemia, constipation, renal failure, electrolyte abnormalities
  - Therapy to lower ammonia concentrations
    - Lactulose, rifaximin, polyethylene glycol, neomycin
- Chronic care
  - Generally continued after first episode
    - Continual lactulose +/- rifaximin
  - Adherence is crucial

Patient Case

70 year old male admitted to the hospital for treatment with lethargy and altered mental status.

- PMH: Significant for cirrhosis secondary to alcohol use x 30 years, esophageal varices, ascites, HTN, osteoporosis, edema
- Home meds: propranolol 20 mg twice daily, calcium/vitamin D chewable supplement, furosemide 40 mg, spironolactone 12.5 mg
- Relevant labs:
  - Serum ammonia: 134 mcg/dL (10-80 mcg/dL ref)
  - Potassium: 3.0 mmol/L
  - SrCr 1.7 mg/dL (baseline 1.3 mg/dL)

Patient Case

What pharmacological interventions should we make at this time?

Patient is now hemodynamically stable with no evidence of cirrhotic decompensation. The team would like your input regarding discharge medications for HE. What do you say?

Summary of Complications

- Portal hypertension
  - Cause behind ascites and variceal formation
- Ascites
  - Management includes diuretics, sodium restriction, alcohol cessation, and paracentesis
- SBP treatment
  - 3rd generation cephalosporin
- Esophageal varices
  - Hemorrhage prophylaxis with NSBB
- Acute variceal hemorrhage
  - Management with octreotide
- Infection prophylaxis
  - Bactrim agent of choice for SBP prophylaxis
- Hepatic encephalopathy
  - Lactulose +/- rifaximin for acute and chronic management

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