Hepatopulmonary Syndrome: A Student Handout for Nephrologists and PA Students

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Learning Objectives

By the end of this session, you should be able to: 1. **Define** hepatopulmonary syndrome (HPS) and recognize its triad of diagnostic criteria 2. **Explain** the pathophysiology of intrapulmonary vascular dilatations and right-to-left shunting 3. **Recognize** the clinical presentation of orthodeoxia and platypnea 4. **Use** contrast-enhanced transthoracic echocardiography (CE-TTE) to screen for HPS 5. **Interpret** severity classification (mild, moderate, severe, very severe) based on oxygenation 6. **Understand** why HPS is an independent indication for MELD exception points 7. **Discuss** the implications of HPS + hepatorenal syndrome (HRS) for transplant candidacy and dialysis management

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Why Nephrologists Need to Know About HPS

You Will Encounter HPS In:

1. **Simultaneous liver-kidney transplantation (SLKT) evaluation** — HPS may affect transplant candidacy
2. **Dialysis patient with cirrhosis** — HPS worsens hypoxemia during volume shifts; need specialized management
3. **Perioperative management** — Liver transplant recipients with acute kidney injury; HPS complicates anesthesia
4. **Multidisciplinary cirrhosis care** — Hepatorenal syndrome + HPS create complex management challenges

Prevalence

- **5-32%** of liver transplant candidates (varies by diagnostic criteria used)
- More common than initially appreciated
- Often undiagnosed until late stages
- Present in ~13% of patients with cirrhosis

The Diagnostic Triad of HPS

All three components are required for diagnosis:

1. Liver Disease (Portal Hypertension ± Cirrhosis)

- Any stage of liver disease with portal hypertension
- Can occur with or without cirrhosis
- Examples: Cirrhosis (any etiology), portal vein thrombosis, non-cirrhotic portal hypertension

2. Intrapulmonary Vascular Dilatations (IPVDs)

- **Abnormal dilation** of pulmonary precapillary and capillary vessels
- Normal vessel diameter: **8-15 µm**
- In HPS: **15-500 µm** (grossly dilated)
- **Confirmed by:**
  - **Contrast-enhanced transthoracic echocardiography (CE-TTE)** — gold standard, >95% sensitivity
  - **99mTc-MAA (technetium-99m macroaggregated albumin) lung perfusion scan** — measures shunt fraction

3. Impaired Oxygenation (At Rest, Room Air)

- **Partial pressure of oxygen (PaO2) <80 mmHg** on room air at sea level, **OR**
- **Alveolar-arterial oxygen gradient (A-a gradient) ≥15 mmHg** (≥20 mmHg if age >64)

Clinical Pearl: Do NOT rely on SpO2 alone! Pulse oximetry can be falsely reassuring. You MUST check arterial blood gas (ABG) to diagnose HPS.

Severity Classification

HPS is stratified by the degree of oxygenation impairment, which drives **urgency of transplantation**:

HPS Grade	PaO2 (mmHg)	A-a Gradient	Clinical Significance
Mild	80-100	≥15	Minimal symptoms; observe; not transplant urgency
Moderate	60-79	≥15	Dyspnea on exertion; consider transplant; can wait weeks-months
Severe	50-59	≥15	Dyspnea at rest; transplant urgency increases; MELD exceptions given
Very Severe	<50	≥15	Profound hypoxemia; high perioperative mortality risk; complex decision-making

Clinical Tip

Very severe HPS (PaO_2 <50) may actually **contraindicate** complex transplantation like SLKT. The perioperative mortality risk can exceed 30%. Isolated liver transplantation is safer but still risky.

Pathophysiology: How Dilated Vessels Cause Hypoxemia

The Three Mechanisms of Oxygen Impairment

1. Diffusion Limitation

- Oxygen **cannot diffuse** from dilated vessel lumen to RBCs in the center of the vessel
- Normal capillaries: Small diameter allows fast diffusion
- Dilated vessels (15-500 μm): Too large; oxygen can't reach the center of the capillary
- Result: Red blood cells transit through without picking up oxygen

2. Intrapulmonary Right-to-Left Shunt

- Some blood **bypasses ventilated alveoli** entirely via dilated vessels
- Like having blood flow through a direct arteriovenous communication in the lung
- This shunted blood is **never oxygenated** regardless of supplemental O_2
- Contributes to refractory hypoxemia

3. Ventilation-Perfusion Mismatch

- IPVDs preferentially develop in **lung bases** (dependent zones)
- When upright, gravity increases perfusion to bases where dilated vessels predominate
- Blood preferentially flows through dilated vessels with impaired gas exchange
- Result: Mismatch between ventilation (top/bases) and perfusion (predominantly bases)

Molecular Mechanisms Driving IPVD Formation

The liver overproduces:

Substance	Effect	Result
Endothelin-1 (ET-1)	Activates ETB receptors on pulmonary endothelium	Increased NO synthesis
Nitric Oxide (NO)	Potent vasodilator	Pulmonary vasodilation, IPVD formation
Carbon Monoxide (CO)	From heme oxygenase-1 activation	Additional vasodilation
VEGF	Vascular endothelial growth factor	Angiogenesis, new abnormal vessel formation
TNF-α	From bacterial translocation	Systemic inflammation, endothelial dysfunction

Net Result: Progressive, diffuse pulmonary vascular dilatation.

Orthodeoxia and Platypnea: The Classic Clinical Sign

Orthodeoxia

Definition: Hypoxemia that **worsens in the upright position** and **improves when supine** (lying flat).

Mechanism: - IPVDs concentrate in lung bases - **Upright position** ☐ Gravity increases perfusion to bases ☐ More blood flows through dilated vessels ☐ Greater shunting ☐ Worse O2 uptake - **Supine position** ☐ Gravity redistributes perfusion more evenly ☐ Less preferential flow through basal dilated vessels ☐ Better oxygenation

Clinical Example: - Seated SpO2 = 88% and dyspneic - Lying supine SpO2 = 94% and breathing easier

Platypnea

Definition: Dyspnea that **worsens in upright position** and improves when lying down.

This is orthodeoxia's clinical companion — the symptom that goes with the oxygenation worsening.

Why This Matters

- **If you see orthodeoxia + platypnea in a cirrhotic patient with hypoxemia, think HPS immediately**
- This is highly specific for HPS (not seen in typical pulmonary hypertension, ILD, or ARDS)
- Ask patients: "Does your breathing feel worse when you sit up?" If yes, check ABG with patient supine vs. sitting

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Diagnostic Workup

Step 1: Suspect HPS in a Cirrhotic Patient With Hypoxemia

You should obtain arterial blood gas (ABG) and measure A-a gradient in any patient with: - **Cirrhosis + dyspnea** - **Portal hypertension + abnormal saturation** - **Hypoxemia that seems out of proportion** to lung findings on exam/X-ray - **Positional dyspnea** (worse upright, better supine)

Step 2: Confirm Oxygenation Impairment

Arterial Blood Gas (ABG): - Measure **PaO2** and calculate **A-a gradient** = (PAO2 - PaO2) - PAO2 = (FiO2 × [Pbaro - PH2O]) - (PaCO2 / RQ) - At sea level, room air: PAO2 ≈ 150 - (PaCO2/0.8) - HPS diagnosed if: **PaO2 <80 mmHg OR A-a ≥15 (≥20 if age >64)**

Step 3: Detect Intrapulmonary Vascular Dilatations

Contrast-Enhanced Transthoracic Echocardiography (CE-TTE) — Gold Standard

- **Procedure:** Agitated saline "bubble study"
  - Inject agitated normal saline intravenously
  - Microbubbles created (diameter >10 μm) are normally **trapped in pulmonary capillaries**
  - Normally: Bubbles appear in right heart ☐ disappear before reaching left heart
- **In HPS:** Dilated vessels allow bubbles to pass through
  - Bubbles appear in **left atrium >3 cardiac cycles** after right heart opacification
  - **Sensitivity >95%** for detecting IPVDs
  - Specific for right-to-left shunt

99mTc-MAA Lung Perfusion Scan

- Particles (20-50 μm) normally trapped in pulmonary vascular bed
- In HPS, particles bypass lungs and accumulate elsewhere (especially brain)
- **Brain uptake >6%** suggests significant shunting
- Can estimate **shunt fraction** quantitatively
- Less sensitive than CE-TTE but quantifies severity

Step 4: Classify by Severity

Once HPS is confirmed, use **PaO2 or A-a gradient** to assign grade (mild/moderate/severe/very severe).

Clinical Presentation

Symptoms

System	Symptoms
Respiratory	Dyspnea on exertion (mild HPS) ☐ dyspnea at rest (severe); orthodeoxia; platypnea
Cardiovascular	Palpitations (high output state); syncope (if PaO2 <50)
Neurologic	Headache; dizziness; confusion (from hypoxemia)
Constitutional	Fatigue (chronic hypoxemia)
Gastrointestinal	Symptoms of underlying liver disease: ascites, variceal bleeding, encephalopathy

Physical Examination

Finding	Meaning
Cyanosis (lips, fingers)	Chronic hypoxemia
Digital clubbing	Chronic hypoxemia
Spider telangiectasias, palmar erythema	Stigmata of cirrhosis
Ascites, splenomegaly	Portal hypertension
Normal lung exam	Key point! Rales/rhonchi would suggest pulmonary disease other than HPS
Murmur	Rarely present in HPS

Laboratory/Imaging

- **ABG:** PaO2 <80, elevated A-a gradient
- **CXR:** Usually **normal or near-normal** — this is a vascular disease, not parenchymal
- **Pulmonary Function Tests:** Reduced DLCO (diffusing capacity), normal FEV1/FVC
- **Echo:** RV dilatation possible; RV systolic pressure normal to mildly elevated (unlike pulmonary arterial hypertension)

Management

The Fundamental Reality

Liver transplantation is the ONLY definitive treatment for HPS. - PaO2 improvement occurs in 80-85% of transplant recipients **within 6-12 months** - No pharmacologic agent has proven consistently effective

What Doesn't Work (Important to Know)

Despite trials, these agents have **NOT shown sustained benefit:** - Inhaled nitric oxide - Methylene blue - Garlic - Pentoxifylline - Somatostatin - Mycophenolate

> **Teaching Point:** Don't waste time on these. Transplant evaluation is the priority.

Why HPS Gets MELD Exception Points

The MELD score (Model for End-Stage Liver Disease) predicts transplant urgency based on bilirubin, INR, and creatinine. But HPS patients can have **normal synthetic function** and low MELD scores yet face **high mortality from hypoxemia alone**.

Therefore: HPS is an **independent indication for MELD exception points** if: - **PaO2 <60 mmHg** on room air at sea level - Documented intrapulmonary vascular dilatations - Evaluation for liver transplantation underway

This gives HPS patients **priority on transplant waiting lists** because their hypoxemia, not their liver biochemistry, drives mortality.

Perioperative Management (Bridge to Transplant)

While waiting for transplant, manage HPS supportively:

Intervention	Rationale
Supplemental oxygen	Increases inspired O2; may help some (but won't correct shunt)
Position upright as tolerated	Improves V/Q matching in some patients
Avoid volume overload	Fluid shifts worsen V/Q mismatch
Monitor closely	Watch for decline; adjust oxygen as needed
Anticoagulation if DVT risk	Normal heparin dosing; dialysis patients need adjusted regimens

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HPS + Hepatorenal Syndrome: A Complex Scenario

When HPS occurs **alongside HRS**, several issues arise:

1. Dialysis Management Becomes Challenging

- **Volume shifts during HD** can worsen V/Q mismatch ☐ acute hypoxemia
- Patient already hypoxic at baseline; dialysis can tip them into crisis
- **Solution:** Consider continuous modalities (CRRT, peritoneal dialysis) for more gradual solute/fluid removal

2. Transplant Candidacy Worsens

- **Very severe HPS (PaO2 <50)** + **HRS** = very high perioperative risk
- Simultaneous liver-kidney transplantation (SLKT) may be too risky
- Single-organ liver transplant alone may be preferred
- Kidney function usually recovers post-liver transplant if HRS was the cause

3. Anesthesia Risk is Increased

- Intubation increases hypoxemia risk
- Prone positioning (some surgeries) worsens orthodeoxia
- Careful anesthesia planning with pulmonology input is essential

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Key Clinical Pearls

1. **Orthodeoxia + platypnea in cirrhosis = HPS until proven otherwise.** This is the clinical clue.
2. **Don't trust SpO2 alone.** Get an ABG. SpO2 may be 94% while PaO2 is 65 due to the way oxygen-hemoglobin curves work.
3. **A normal CXR doesn't rule out HPS.** The lungs look normal because IPVDs are vascular, not parenchymal. That's a key distinguishing feature.
4. **Mild HPS (PaO2 80-100) may progress.** Follow-up ABGs every 3-6 months; watch for decline.

5. **Very severe HPS (PaO2 <50) carries high surgical mortality.** Be frank with patients about transplant risks.
6. **Liver transplant is curative.** Most patients improve significantly by 6-12 months post-transplant. This is the goal.
7. **HPS + HRS is deadly.** Manage conservatively; prioritize for transplant urgently.
8. **Pulmonary hypertension != HPS.** In pulmonary arterial hypertension (PAH), RV pressure is high (mean PAP >25 mmHg); in HPS, pulmonary pressures are normal-to-low. Different diseases, different treatments.

Comparison Table: HPS vs. Other Causes of Hypoxemia in Cirrhosis

Diagnosis	CXR	DLCO	A-a Gradient	Orthodeoxia	CE-TTE	Treatment
HPS	Normal	☐	≥15	Present	Delayed bubbles	Transplant
IPH	Infiltrates	☐	☐	Absent	Neg	Diuretics, antibiotics
PAH	Normal	☐	☐	Absent	High RV pressure	Pulmonary vasodilators
Pulmonary Edema	Infiltrates	Normal	☐	Absent	Normal pressures	Diuretics, vasodilators
Pleural Effusion	Effusion	May ☐	☐	Absent	Normal	Treat underlying cause

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Practice Questions

Question 1: Case Presentation

A 62-year-old woman with cirrhosis (Child-Pugh B) presents with progressive dyspnea over 6 months. She reports her shortness of breath is **much worse when sitting up** but improves dramatically when she lies down. Physical exam shows ascites and spider telangiectasias but **clear lungs**. CXR is normal. Resting SpO2 = 92%.

Which test should you order next to evaluate for HPS?

A. Pulmonary function testing (PFTs) B. Arterial blood gas (ABG) with patient both seated and supine C. High-resolution CT chest D. Right heart catheterization

Answer: B. This patient has classic **orthodeoxia and platypnea** (dyspnea worse upright, better supine). You must confirm the oxygenation impairment with ABG and calculate the A-a gradient. The positional nature strongly suggests HPS. ABG is the first confirmatory step. (PFTs come later; HRCT not needed; RHC would show normal pressures in HPS, not the elevated pressures of PAH.)

Question 2: Mechanism Question

A patient with HPS and PaO2 = 58 mmHg is given supplemental oxygen (FiO2 100% by non-rebreather). His PaO2 improves to 62 mmHg. This minimal response to high-concentration oxygen is best explained by:

A. Hypoventilation from encephalopathy B. Intrapulmonary right-to-left shunting through dilated vessels — oxygen can't reach the shunted blood C. Pulmonary fibrosis preventing oxygen diffusion D. Anemia reducing oxygen-carrying capacity

Answer: B. **This is the key principle of HPS:** A true right-to-left shunt (blood bypassing ventilated alveoli) does NOT respond well to supplemental oxygen because the shunted blood is never exposed to high-oxygen air. In contrast, V/Q mismatch or hypoventilation **improves** with supplemental O2. The relative lack of response to high FiO2 is actually diagnostic of a significant shunt, which is characteristic of HPS.

Question 3: Management Question

A 55-year-old man with cirrhosis is found to have HPS with PaO2 = 68 mmHg and documented IPVDs on CE-TTE. He is not a transplant candidate due to advanced hepatocellular carcinoma (HCC) beyond transplant criteria. He remains short of breath despite supplemental oxygen.

What is the most appropriate next step?

A. Start inhaled nitric oxide therapy B. Start a pulmonary vasodilator (sildenafil) C. Refer to palliative care; optimize comfort; discuss prognosis D. Start albumin dialysis (MARS system)

Answer: C. This is a **prognostically difficult situation.** Without transplant as an option, pharmacologic therapies for HPS lack strong evidence and don't alter the trajectory. The compassionate approach is **palliative care** focus: optimize symptom control (oxygen), discuss realistic prognosis (HPS without transplant carries high mortality), and ensure the patient's values/wishes are understood. (Nitric oxide and sildenafil lack robust data; MARS is investigational.)

Summary: HPS at a Glance

Concept	Key Point
Definition	Triad: liver disease + intrapulmonary vascular dilatations + hypoxemia
Prevalence	5-32% of transplant candidates
Pathophysiology	IPVDs cause diffusion limitation, R☐L shunt, V/Q mismatch
Classic Sign	Orthodeoxia + platypnea (dyspnea worse upright, better supine)
Diagnosis	CE-TTE (>95% sensitivity); PaO2 <80 OR A-a ≥15 (≥20 if age >64)
Severity	Mild (PaO2 80-100) ☐ Moderate (60-79) ☐ Severe (50-59) ☐ Very Severe (<50)

Concept	Key Point
Prognosis	Untreated: progressive decline; Transplanted: 80-85% improve in 6-12 months
Treatment	**Liver transplantation only definitive therapy**; supportive care while waiting
MELD Exception	Yes, if PaO2 <60 mmHg; elevates transplant priority
With HRS	Complex case; SLKT vs. isolated liver transplant; increased perioperative risk

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References & Further Reading

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