Could a fat-derived molecule help explain why the immune system becomes weaker in advanced cirrhosis?

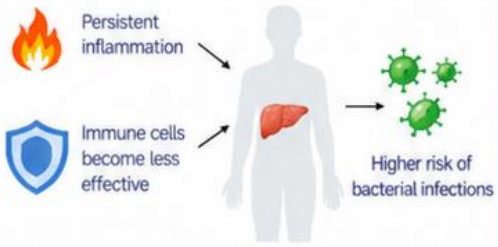
People with advanced cirrhosis can have **high systemic inflammation** while their immune system becomes **less able to fight infections**. Why does this happen?

MICROB-PREDICT

Researchers from **MICROB-PREDICT** identified a molecule called **9,10-DiHOME** that may help explain this problem.

Found at higher levels in patients who developed acute-on-chronic liver failure **(ACLF)** – a sudden deterioration of advanced cirrhosis with one or more organ failures – and bacterial infections, and shown in the lab to weaken key immune-cell functions.

1 First, what happens to the immune system in advanced cirrhosis?



Infections can trigger further deterioration and contribute to the development of **ACLF**.

2 What is 9,10-DiHOME?

A **lipid mediator** – a small molecule derived from fats that influences how cells behave.

Produced from **linoleic acid** (an omega-6 fatty acid) through chemical reactions in the body.

One key enzyme in this pathway is **soluble epoxide hydrolase (sEH)**.

Researchers wanted to know if changes in these molecules drive the abnormal immune response in advanced cirrhosis.

3 What did the researchers do?

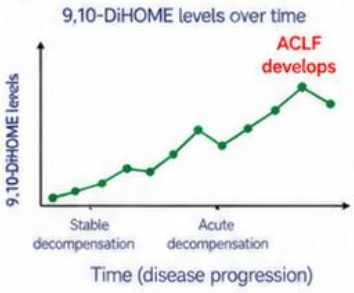
Studied **308** plasma samples from **93** patients with acutely decompensated cirrhosis (with and without ACLF) and **31** healthy individuals.

Analysed **98** different lipid mediators.

Performed laboratory experiments on immune cells to understand what 9,10-DiHOME does.

Tested whether blocking the enzyme that produces 9,10-DiHOME could improve immune responses in mice with cirrhosis.

4 What did they find?



Levels higher in patients with ACLF than without ACLF.

Levels increased as patients progressed towards ACLF and peaked around the time ACLF developed.

Higher pathway activity seen with **bacterial infections**.

Important: 9,10-DiHOME did not show statistically significant predictive value for determining who would develop ACLF or bacterial infection. It is not a predictive clinical biomarker.

5 How may 9,10-DiHOME weaken the immune system?

In certain white blood cells, it:

Reduced release of substances used to attack pathogens

Reduced oxidative response against pathogens

Reduced **phagocytosis** (engulfing bacteria)

In other immune cells, it:

Increased MerTK (an immunosuppressive marker)

Reduced ability to produce immune signalling molecules in response to bacterial components

In simple terms, 9,10-DiHOME pushes parts of the immune system towards a less effective defensive state.

6 Could researchers block this process?

Researchers focused on **sEH**, the enzyme that produces 9,10-DiHOME.

In mice with cirrhosis, they used an experimental drug to inhibit sEH.

Blocking sEH reduced circulating 9,10-DiHOME.

Macrophages shifted from an immunosuppressive state to a more active immune phenotype.

MerTK expression in liver macrophages was also reduced.

Proposed mechanism

↑ 9,10-DiHOME

↓

Weakened immune cell functions

↓

Blocking sEH

↓

Restored immune function (in mice)

7 What could this mean for patients?

Provides a possible explanation for why patients have strong inflammation but weaker defences against infections.

9,10-DiHOME could be part of the puzzle.

The pathway could become **a new therapeutic target** in the future.

Goal: restore the body's own immune defences in high-risk patients.

Potentially moving from only treating infections to preventing the immune dysfunction that makes patients vulnerable.

But this is still experimental.

8 Is there a new treatment for patients?

No.

Benefits of blocking sEH were shown in mice, not in humans.

Many questions remain about safety and effectiveness in people with advanced cirrhosis.

Clinical studies are needed before this approach could become a treatment.

9 What is the bigger picture?

Moves beyond observation to identify a specific biological pathway behind immune dysfunction in advanced cirrhosis.

Identifies a part of that pathway that could potentially be targeted with future therapies.

The study suggests that increased **9,10-DiHOME** may contribute to the weakened immune defences seen in advanced cirrhosis and ACLF. Blocking the enzyme responsible for producing it could potentially offer a new way to restore immune function – but this approach still needs to be tested in humans.

10 About the research

Title of Publication: "The linoleic acid-derived leukotoxin, 9,10-DiHOME drives immunosuppression in patients with acute-on-chronic liver failure."

Conducted by Contreras and colleagues from the MICROB-PREDICT consortium.

Contreras BJ et al. (2026) The linoleic acid-derived leukotoxin 9,10-DiHOME drives immunosuppression in patients with acute-on-chronic liver failure Hepatology: Online ahead of print.

The MICROB-PREDICT project received funding from the European innovation programme (No. 825694).