ACUTE-ON-CHRONIC LIVER FAILURE

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- Acute-on-chronic liver failure (ACLF) is a syndrome characterised by acute decompensation of chronic liver disease associated with organ failures and high shortterm mortality
- Alcohol and chronic viral hepatitis are the most common underlying liverdiseases.

- Sepsis, active alcoholism and relapse of chronic viral hepatitis are the most common reported precipitating factors.
- An excessive systemic inflammatory response seems to play a crucial role in thedevelopmentof ACLF

Aetiologyof chronic liver disease inACLF

- Viral hepatitis, alcohol or a combination of both are the predominant causes of underlying chronic liver disease in ACLF in theworld.
- non-alcoholic steatohepatitis took the lead in years to come.

Triggers of decompensation inACLF

- bacterial infections and alcoholism are the two major identifiable factors, compared with China, where relapse of hepatitis B was predominant followed by bacterial infections
- in 20%–45% of cases, the trigger remains unknown.

Organ failure

- the kidneys were the most common affected organs (55.8% of patients), followed by the liver (43.6% of patients), coagulation (27.7% of patients), the brain (24.1% of patients), circulation (16.8% of patients) and the lungs (9.2% of patients).

PATHOPHYSIOLOGY OF SYSTEMIC INFLAMMATION INACLF

- Systemic inflammation is a hallmark of ACLF; white cell count and plasma levels of C reactive protein (CRP) and pro-inflammatory molecules such as interleukin (IL)-6, IL-1β, IL-8 are higher in patients with ACLF than in those without.

ACLF with identified inducersof Inflammation

- Sepsis-induced ACLF: Systemic inflammation and the development of OFs are attributed to bacterial infection in approximately 30% of patients withACLF
- The most common infection causing sepsis-inducedACLF is spontaneous bacterial peritonitis(SBP)
- SBP is a paradigm in that it is often caused by Gram-negative bacteria that have migrated from the intestinal lumen to ascitic fluid via the systemiccirculation.

- Severe alcoholic hepatitis (SAH) represents approximately 25% of the cases ofACLF
- About 40%–50% of patients with ACLF have systemic inflammation for which there are no clinically identifiable triggers

DIAGNOSIS

- ACLF is defined as acute decompensation (AD) of cirrhosis associated with OF and high short-term mortality (28-day mortality ≥15%)
- The SOFA score (sequential organ failure assessment) was the model used for the diagnosis of OF, as it is a widely used method in critically ill patients and is superior to Model For End-Stage Liver Disease (MELD) score in predicting prognosis in patients with AD of cirrhosis associated withOFs

Sequential [Sepsis-Related] Organ Failure Assessment (SOFA) Score

System	0	1	2	3	4
Respiration PaO2/FiO2, mmHg (kPa)	≥400 (53.3)	<400 (53.3)	<300 (40)	<200 (26.7) with respiratory support	<100 (13.3) with respiratory support
Coagulation Platelets, x10³/uL	≥150	<150	<100	<50	<20
Liver Bilirubin, mg/dL (umol/L)	<1.2 (20)	1.2 - 1.9 (20 - 32)	2.0 - 5.9 (33 - 101)	6.0 - 11.9 (102 - 204)	>12.0 (204)
Cardiovascular	MAP ≥70mmHg	MAP <70mmHg	Dopamine <5 or Dobutamine (any dose)	Dopamine 5.1 - 15 or Epinephrine ≤0.1 or Norepinephrine ≤0.1	Dopamine >15 or Epinephrine >0.1 or Norepinephrine >0.1
CNS GCS Score	15	13 - 14	10 -12	6 - 9	<6
Renal Creatinine, mg/dL (umol/L) Urine Output, mL/d	<1.2 (110)	1.2 - 1.9 (110 - 170)	2.0 - 3.4 (171 - 299)	3.5 - 4.9 (300 - 440) <500	>5.0 (440) <200
*Catecholamine Doses = ug/kg/min for at least 1hr					

SOFA Score	Mortality if initial score	Mortality if highest score
0-1	0.0%	0.0%
2-3	6.4%	1.5%
4-5	20.2%	6.7%
6-7	21.5%	18.2%
8-9	33.3%	26.3%
10-11	50.0%	45.8%
12-14	95.2%	80.0%
>14	95.2%	89.7%

MANAGEMENT OFACLF

- Currently, there is no specific effective treatmentavailable forpatients with ACLF, and therefore treatment is based on organ support and treatment of associated complications.
- When ACLF is associated with a precipitating factor (ie, bacterial infections, GI bleeding, alcoholism, drug toxicity), early identification and treatment of the precipitating factor areessential.
- patients with ACLF should be considered to beadmitted to the ICU and should be preferably managed in a transplantcentre

Specific therapies

- Livertransplantation

LT represents the definitive treatment for patients with ACLF if there are nocontraindications

- Liver supportsystems

Extracorporal liver support systems, particularly albumin dialysis and/or plasma exchange have been proposed as new therapeutic options that could be used as a bridge to LT in patients with ACLF

Future perspectives

- Pathophysiologial-basedtreatments

- Bacterial translocation (BT) and an excessive systemic inflammation are the key mechanisms leading to the progression of cirrhosis and the development of ACLF.

-Therapeutic interventions acting on BT (ie, probiotics, norfloxacin, rifaximin) would probably act in the prevention of the development of ACLF rather than in the management of the syndrome itself once it has developed

- innovative therapies based on immunomodulatory or liver regenerative effects have been proposed as new therapeutic approaches, including administration of granulocyte-colony stimulating factor (G-CSF) and stem celltransplantation.

SUMMARY

- once ACLF have occurred, the following days will determine whether the patient will undergo recovery or not with full medical support including evaluation for liver transplant (tertiary prevention).
- One organ has failed and the aim is to prevent further OF involvement by providing aggressive medical care (eg, antibiotics to prevent hepatorenal syndrome in the setting of gastrointestinal bleeding(GIB)).
- Preventing other OFs is an example of secondary prevention (damage is present but aiming to reduce furtherdamage).

- Prevention of ACLF should be based on treatments targeting the key pathophysiological mechanisms leading to disease progression and development ofACLF.
- Evidence from the last decade suggests that these key mechanisms are mainly the impairment of the gut-liver axis leading to BT and systemicinflammation.
- Therefore, therapeutic interventions targeting BT and those modulating inflammatory response (ie, norfloxacin, rifaximin, albumin, statins) should be investigated as potential first-linetreatments.

- Nguồn tài liệu: Moreau R, et al (2017) “Acute-on-chronic liver failure: an update” *Gut* ;**66**.pp.541–553.