ACUTE ON CHRONIC LIVER FAILURE

When and How to Approach

Juliet L. Gopez-Cervantes, MD
Head, Liver Disease and Transplant Center
St. Luke's Medical Center

INTRODUCTION

ACUTE LIVER FAILURE (ALF)

ACUTE-ON-CHRONIC LIVER FAILURE (ACLF)

CHRONIC DECOMPENSATION OF END-STAGE LIVER DISEASE

Sarin, S.K. et al; "Acute-on-chronic liver failure: Consensus recommendations of the Asian Pacific Association for the study of the liver (APASL)"; Hepatology International; 2009; 3: 269-282.

DEFINITION

	APASL (2009)	EASL-AASLD (2012)
Patient	With previously diagnosed or undiagnosed chronic liver disease (CLD)	With pre-existing chronic liver disease (CLD)
Manifestations	Jaundice & coagulopathy	
Complication	Ascites and/or encephalopathy within 4 weeks	
Cause of mortality		Multi-system organ failure
	Sarin, S.K. et al; "Acute-on-chronic liver failure: Consensus recommendations of the Asian Pacific Association for the study of the liver (APASL)"; Hepatology International; 2009; 3: 269-282.	*Jalan, R. et al; "Acute-on chronic liver failure"; Journal of Hepatology; 2012; vol. 57:1336-1348*

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CANONIC STUDY

CONCLUSION

- ACLF is a distinct syndrome from AD based on the presence of organ failure(s), high mortality rate, age, precipitating events, and systemic inflammation.
- ACLF mortality is associated with loss of organ function and high leukocyte counts.
- ACLF is especially severe in patients with no prior history of AD.

Moreau, R. et al; "Acute on Chronic Liver Failure is a Distinct Syndrome that Develops in Patients with Acute Decompensation of Cirrhosis", Gastroenterology; 2013; 144:1426-1437

DEFINITION

The following are central in the definition of ACLF, whatever the precipitating event:

1. Existence of a precipitating factor
2. Rapid deterioration in liver function
3. Initiation of extra-hepatic organ failure(s)
4. High in-hospital or early mortality (28 days)

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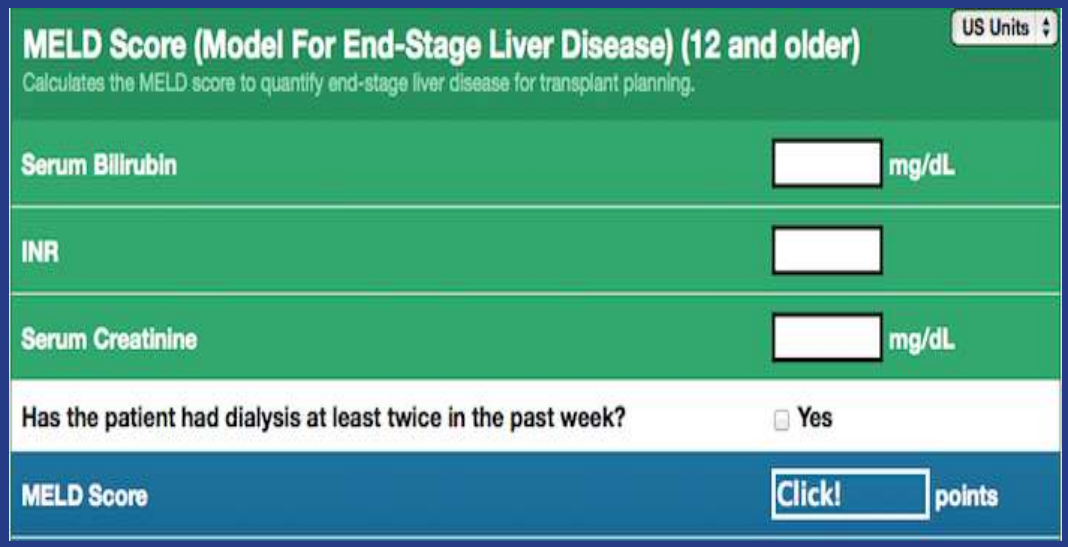
Importance of ACLF



Model for End Stage Liver Disease (MELD)

MELD score= 10x[0.957x log e (creatinine) + log e (bilirubin) + 1.12 x log e (INR)] + 6.43

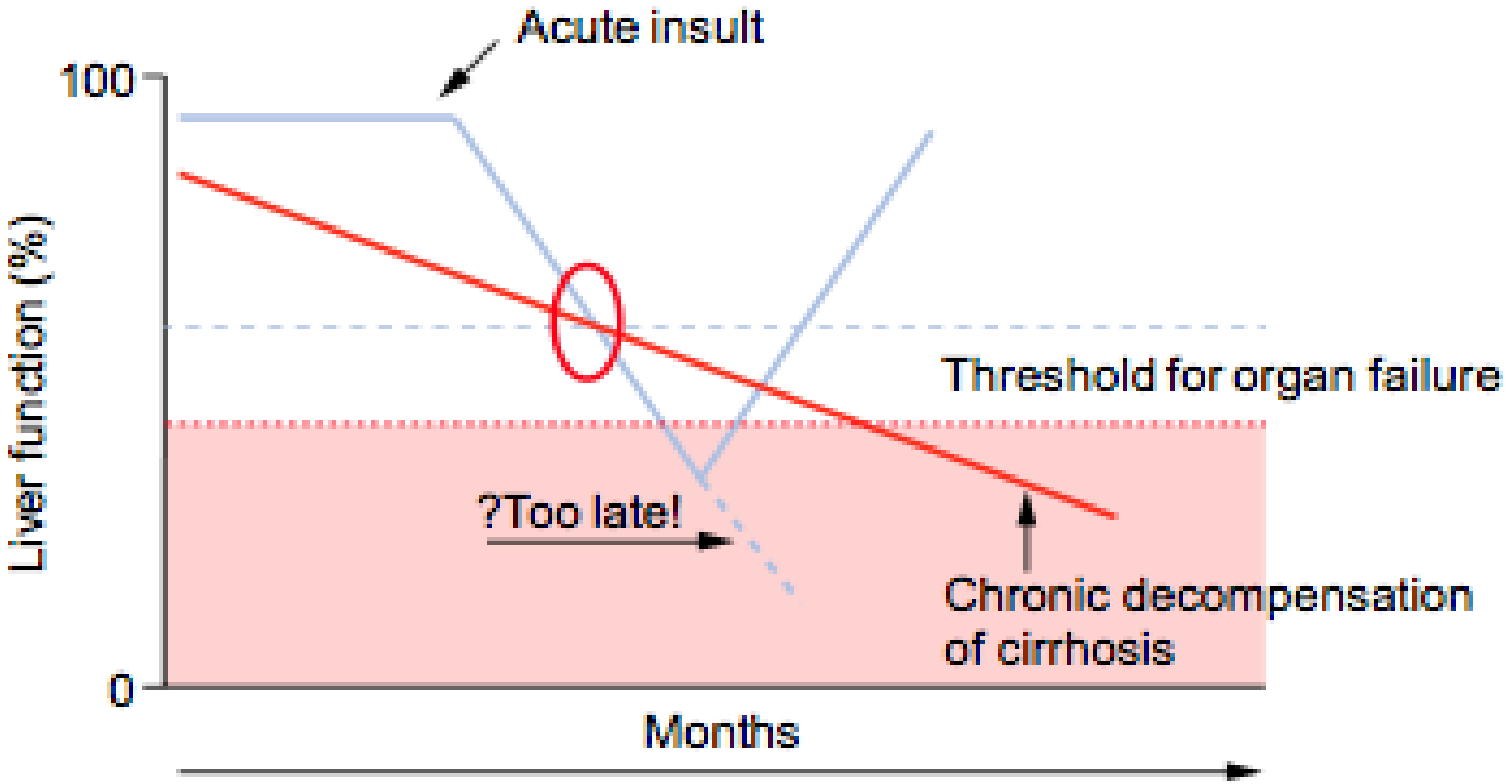
3 month mortality according to MELD score

MELD score	<=9	10-19	20-29	30-39	>=40
Hospitalized pt.	4%	27%	76%	83%	100%
Outpatient cirrhotic	2%	6%	50%		

- MELD score based allocation system in liver transplantation
- Relies on a 'sickest first' policy
- Offers opportunity for ACLF patients to receive an allograft based on disease severity
- Bridges ALCF patients to 'salvage' transplantation

Moreaur, R. and Durand F.; "Acute on Chronic Liver Failure"; 2011

Acute-on chronic liver failure: diagrammatic representation of the clinical concept.



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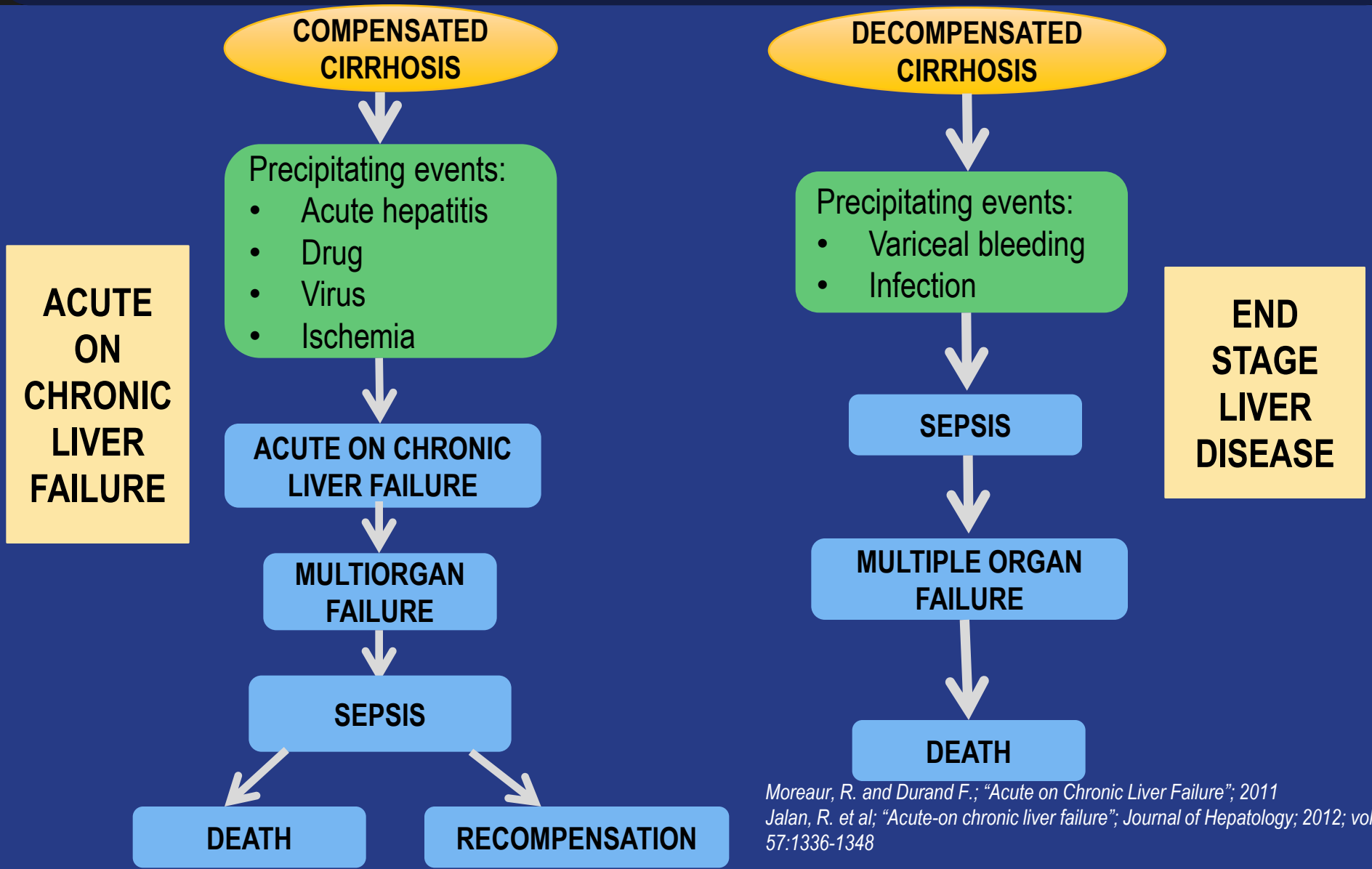
DIFFERENCE BETWEEN ACLF & ESLD (PATHOGENESIS)



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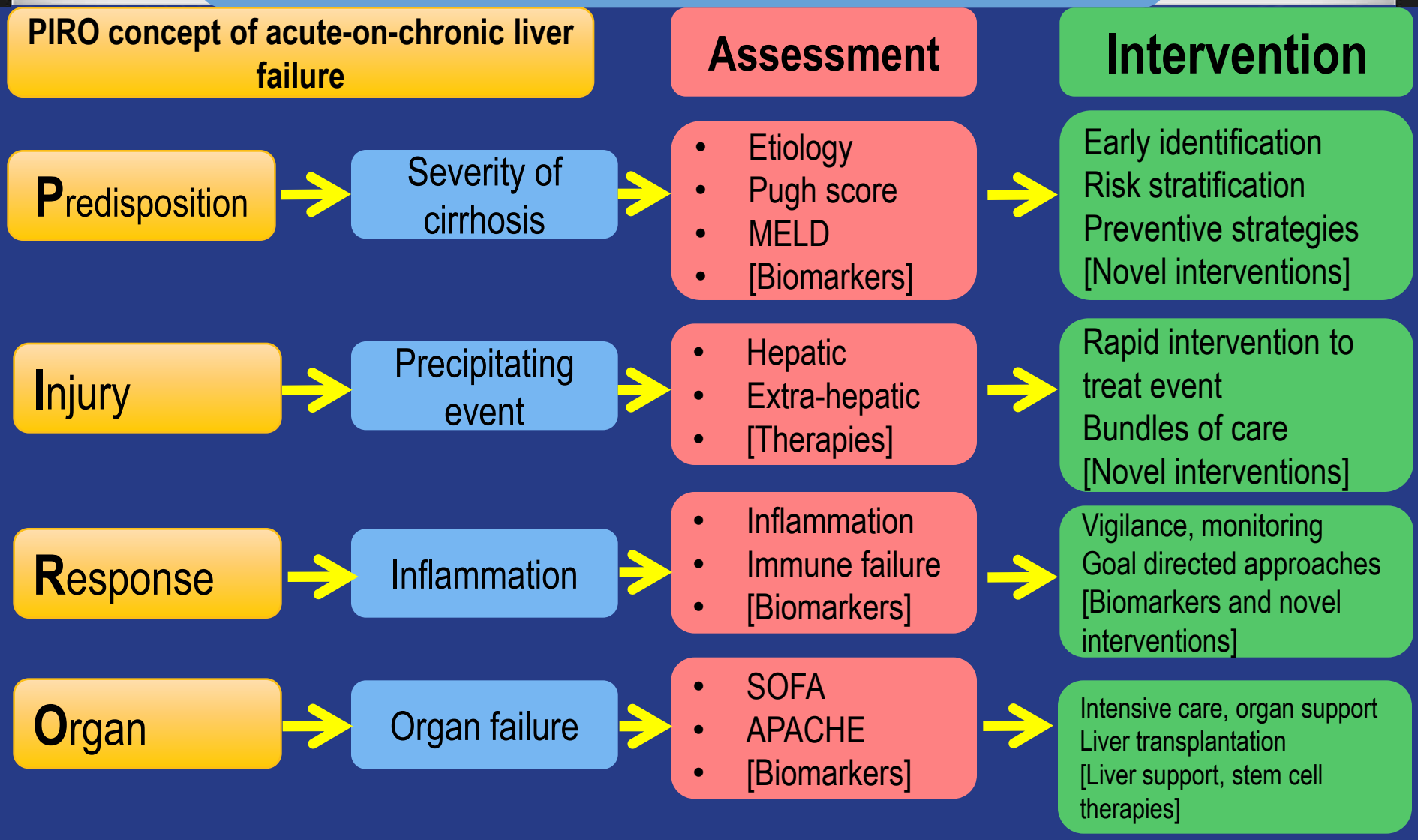
Pathophysiology



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PRECIPITATING EVENTS

EXTRAHEPATIC CAUSES

BACTERIAL SEPSIS

VARICEAL HEMORRHAGE

HEPATIC CAUSES

ALCOHOL

HEPATOTROPIC VIRUSES

DRUG REACTION

Moreaur, R. and Durand F.; "Acute on Chronic Liver Failure"; 2011

REMARKABLE FEATURES OF ACLF

- **Marked persistent systemic inflammatory response (SIRS)**
- associated with activation of the inflammatory cytokine cascade
- Causing transition from stable cirrhosis to ACLF.

- **Proinflammatory cytokines**
- mediate hepatic inflammation, apoptosis and necrosis of liver cells, cholestasis and fibrosis.

- The presence of SIRS is associated with more severe encephalopathy, associated infection, renal failure and poor outcome.
- Central role of inflammation and neutrophil dysfunction in organ failure

Vincent, JL et al; "The Critically Ill Cirrhotic Patient: Pathophysiological Basis: Infection and Inflammation?"; 257-261
Sarin, S.K. et al; "Acute-on-chronic liver failure: Consensus recommendations of the Asian Pacific Association for the study of the liver (APASL)"; Hepatology International; 2009; 3: 269-282.

Immune dysfunction of ACLF

Liver failure / bacterial translocation

- Endotoxemia
- Reduced protein/complement synthesis
- Reduced immune surveillance
- Reduced albumin function

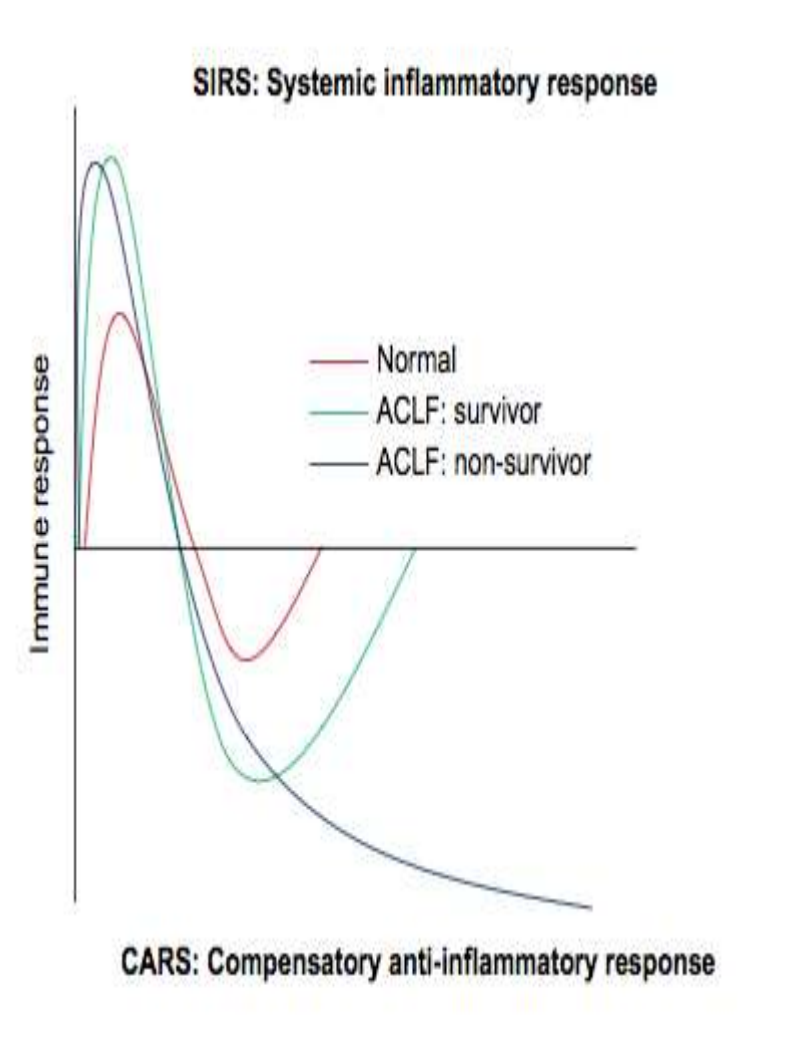
Immune paralysis

Innate immunity

- Neutrophils: phagocytic defect
- Monocytes: DR loss
- NK cells

Adaptive immunity

- T-cell exhaustion
- Inability to proliferate
- Increased apoptosis



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DIAGNOSIS

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DIAGNOSTIC CRITERIA

Child-Turcotte-Pugh Classification for Severity of Cirrhosis			
Clinical and Lab Criteria	Points*		
	1	2	3
Encephalopathy	None	Mild to moderate (grade 1 or 2)	Severe (grade 3 or 4)
Ascites	None	Mild to moderate (diuretic responsive)	Severe (diuretic refractory)
Bilirubin (mg/dL)	< 2	2-3	>3
Albumin (g/dL)	> 3.5	2.8-3.5	<2.8
Prothrombin time			
Seconds prolonged	<4	4-6	>6
International normalized ratio	<1.7	1.7-2.3	>2.3
*Child-Turcotte-Pugh Class obtained by adding score for each parameter (total points)			
Class A = 5 to 6 points (least severe liver disease)			
Class B = 7 to 9 points (moderately severe liver disease)			
Class C = 10 to 15 points (most severe liver disease)			

MELD Score (Model For End-Stage Liver Disease) (12 and older)

US Units

Calculates the MELD score to quantify end-stage liver disease for transplant planning.

Serum Bilirubin		mg/dL
INR		
Serum Creatinine		mg/dL
Has the patient had dialysis at least twice in the past week?	☐ Yes	
MELD Score	Click!	points

The APACHE II Severity of Disease Classification System

Physiologic Variable	High Abnormal Range						Low Abnormal Range		
	+4	+3	+2	+1	0	+1	+2	+3	+4
Temperature - rectal (°C)	≥41°	39 to 40.9°		38.5 to 38.9°	36 to 38.4°	34 to 35.9°	32 to 33.9°	30 to 31.9°	≤29.9°
Mean Arterial Pressure - mm Hg	≥160	130 to 159	110 to 129		70 to 109		50 to 69		≤49
Heart Rate (ventricular response)	≥180	140 to 179	110 to 139		70 to 109		55 to 69	40 to 54	≤39
Respiratory Rate (non-ventilated or ventilated)	≥50	35 to 49		25 to 34	12 to 24	10 to 11	6 to 9		≤5
Oxygenation: A-aDO_2 **or** PaO_2 (mm Hg) a. FIO_2 ≥0.5 record A-aDO2 b. FIO_2 <0.5 record PaO2	≥500	350 to 499	200 to 349		<200 PO2>70	 PO2 61 to 70		 PO2 55 to 60	 PO2<55
Arterial pH (preferred) Serum HCO3 (venous mEq/l) (not preferred, but may use if no ABGs)	≥7.7 ≥52	7.6 to 7.69 41 to 51.9		7.5 to 7.59 32 to 40.9	7.33 to 7.49 22 to 31.9		7.25 to 7.32 18 to 21.9	7.15 to 7.24 15 to 17.9	<7.15 <15
Serum Sodium (mEq/l)	≥180	160 to 179	155 to 159	150 to 154	130 to 149		120 to 129	111 to 119	≤110
Serum Potassium (mEq/l)	≥7	6 to 6.9		5.5 to 5.9	3.5 to 5.4	3 to 3.4	2.5 to 2.9		<2.5
Serum Creatinine (mg/dl) Double point score for acute renal failure	≥3.5	2 to 3.4	1.5 to 1.9		0.6 to 1.4		<0.6		
Hematocrit (%)	≥60		50 to 59.9	46 to 49.9	30 to 45.9		20 to 29.9		<20
White Blood Count (total/mm3) (in 1000s)	≥40		20 to 39.9	15 to 19.9	3 to 14.9		1 to 2.9		<1
Glasgow Coma Score (GCS) Score = 15 minus actual GCS									
A. Total Acute Physiology Score (sum of 12 above points)									
B. Age points (years) <44=0; 45 to 54=2; 55 to 64=3; 65 to 74=5; >75=6									
C. Chronic Health Points (see below)									
Total APACHE II Score (add together the points from A+B+C)									

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DIAGNOSTIC CRITERIA

Table 1. CLIF-SOFA Score

Organ/system	0	1	2	3	4
Liver (bilirubin, *mg/dL*)	<1.2	≥1.2 to ≤2.0	≥2.0 to <6.0	≥6.0 to <12.0	**≥12.0**
Kidney (creatinine, *mg/dL*)	<1.2	≥1.2 to <2.0	**≥2.0 to <3.5**	**≥3.5 to <5.0**	**≥5.0**
				or use of renal replacement therapy	
Cerebral (HE grade)	No HE	I	II	III	IV
Coagulation (international normalized ratio)	<1.1	≥1.1 to <1.25	≥1.25 to <1.5	≥1.5 to <2.5	**≥2.5 or platelet count ≤20×10⁹/L**
Circulation (mean arterial pressure, *mm Hg*)	≥70	<70	**Dopamine ≤5 or dobutamine or terlipressin**	**Dopamine >5 or E ≤0.1 or NE ≤0.1**	**Dopamine >15 or E >0.1 or NE >0.1**
Lungs					
PaO_2/FiO_2 or	>400	>300 to ≤400	>200 to ≤300	**>100 to ≤200**	**≤100**
SpO_2/FiO_2	>512	>357 to ≤512	>214 to ≤357	**>89 to ≤214**	**≤89**

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DIAGNOSTIC CRITERIA

Systemic Inflammatory Response Syndrome (SIRS)

When 2 of the following criteria are met:

- Body temperature >38° C or <36° C
-Heart rate > 90bpm
-Respiratory rate > 20cpm or arterial hypocapnia <32mmHg
-WBC > 12,000/uL or <4,000/uL or immature forms > 10%

American College of Chest Physicians / Society of Critical Care

PROGNOSTIC INDICATORS

Most common promising indicators of ACLF and their association with mortality extracted from 13 studies	
1. AGE	Positively associated with mortality
2. BILIRUBIN	Cut-off: 23.1mg/dL
3. MELD	Cut-off: ≥ 30
4. HEPATIC ENCEPHALOPATHY	
5. INR	Cut-off 1.5 - 2

Wlodzimirow, KA, et al; "A Systematic Review on prognostic indicators of acute on chronic liver failure and their predictive value for mortality."; Liver International; 2012; 40-52

MANAGEMENT

TREATMENT OF THE PRECIPITATING EVENT

- BACTERIAL SEPSIS
- SEVERE ALCOHOLIC HEPATITIS
- ACUTE VARICEAL HEMORRHAGE
- HEPATITIS B VIRUS
- DRUG INDUCED ACLF

MANAGEMENT OF ORGAN FAILURES

- CIRCULATORY FAILURE
- ACUTE RENAL FAILURE
- ADRENAL FAILURE
- RESPIRATORY FAILURE
- HEPATIC ENCEPHALOPATHY / LIVER FAILURE
- COAGULATION FAILURE

Moreaur, R. and Durand F.; "Acute on Chronic Liver Failure"; 2011

Treatment

- Antiviral therapy should be initiated in patients with ACLF due to hepatitis B. (3b, C)
- Lamivudine may be used for a short-term period, but other drugs such as entecavir or tenofovir may be preferred in view of the long-term need for viral suppression with low frequency of drug resistance. (3b, C)

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Treatment

- Prophylactic therapy is recommended for HBsAg-positive patients undergoing chemotherapy. (3b, C)
- There is insufficient data to recommend antiviral therapy for HBsAg-negative and anti-HBc-positive patients. (3b, C)

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Use of liver support devices in ACLF

- Molecular adsorbent recirculating system (MARS) does not offer any survival benefit to patients with ACLF. (1a, A)
- Role of MARS as a bridge to transplantation in patients with ACLF is still to be defined. (2b, B)
- MARS may improve hepatic encephalopathy in patients with ACLF. (1a, A)
- Plasma exchange needs further validation for the treatment of ACLF. (3b, C)

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Liver Transplant in patients with ACLF

Criteria when to transplant
1. Liver transplantation should be performed according to prognosis scores suggesting death within the next 3 months. (2b, B)
2. Earlier intervention if HRS develops. (2b, B)
2.1 Liver transplantation should not be performed when there is HRS with anuria. (3b, C)
2.2 Results of liver transplantation are better when HRS has been partially controlled by terlipressin. (2b, B)

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Liver Transplant in patients with ACLF

Criteria when not to transplant
1. Hemodynamic instability and high-dose inotrope requirement (sepsis, bleeding). (2a, B)
2. Severe bacterial infection. (2a, B)
3. Fungal infection. (2a, B)
4. Cerebral edema or intracranial bleeding. (1a, A)

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CONCLUSION

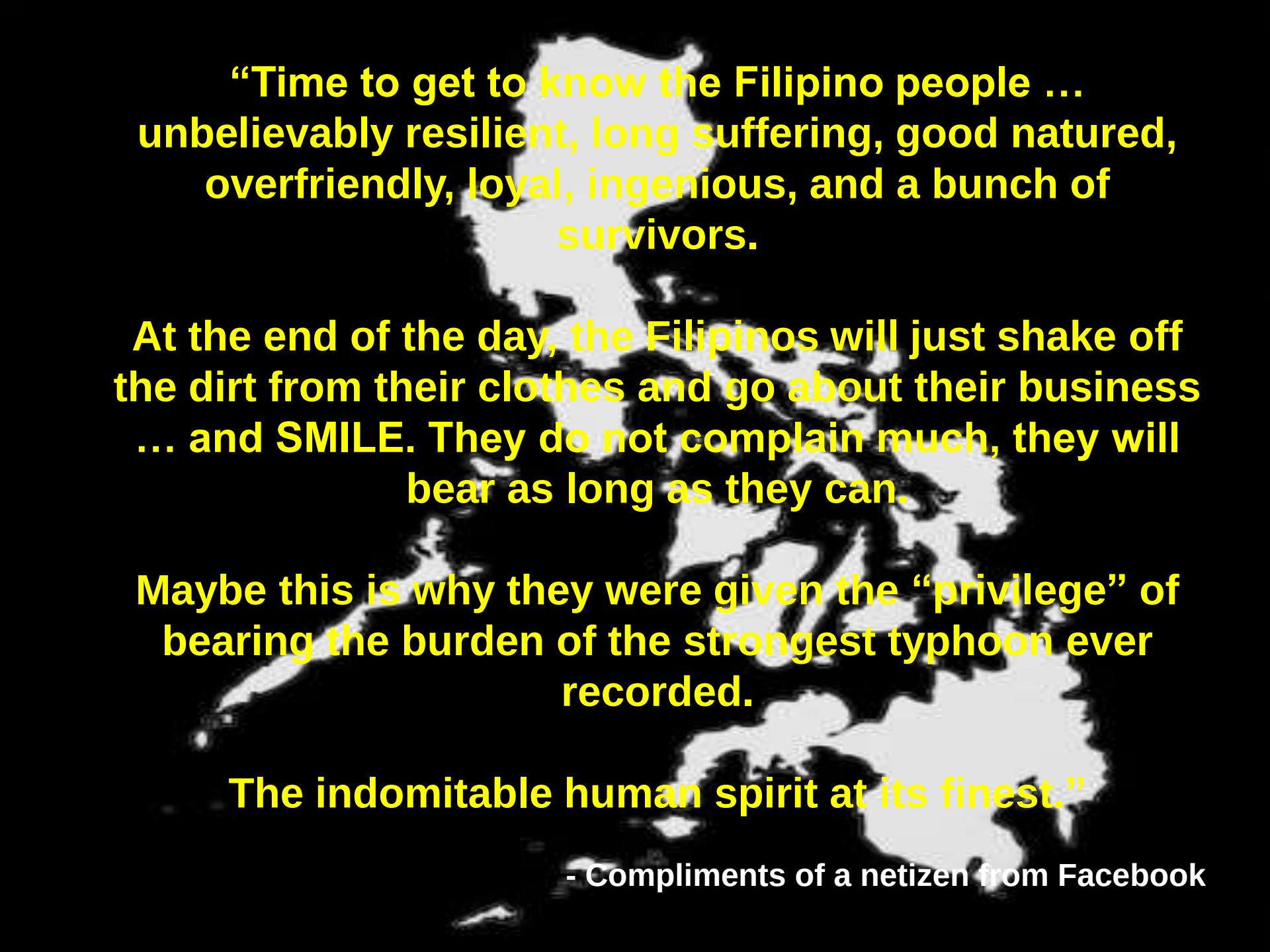
- ACLF is the acute deterioration of liver function in a patient with compensated or decompensated, but stable cirrhosis.
- ACLF is a highly prevalent, life-threatening disease (with higher mortality in a few days or weeks) with few therapeutic options at present.
- It is a potentially reversible complication of chronic liver disease if caught at an early stage.

CONCLUSION

- Precipitating acute events: bacterial infection,variceal hemorrhage or primary liver insult due to alcohol, virus, drugs
- It is associated/coincides with failure of extra-hepatic organs.
- Inflammation is the LINK between the triggering event and the development of organ failure.

CONCLUSION

- There is still NO established universally acceptable diagnostic criteria as of date
- Management includes treatment of the precipitating event and of organ failure(s), and eventually liver transplantation.
- Early recognition of the syndrome with a more pathophysiology-guided therapeutic approach results in better survival rates of patients with ACLF, reducing the need for liver grafts as an ultimate salvage therapy.



"Time to get to know the Filipino people … unbelievably resilient, long suffering, good natured, overfriendly, loyal, ingenious, and a bunch of survivors.

At the end of the day, the Filipinos will just shake off the dirt from their clothes and go about their business … and SMILE. They do not complain much, they will bear as long as they can.

Maybe this is why they were given the "privilege" of bearing the burden of the strongest typhoon ever recorded.

The indomitable human spirit at its finest."

- Compliments of a netizen from Facebook

THANK YOU!