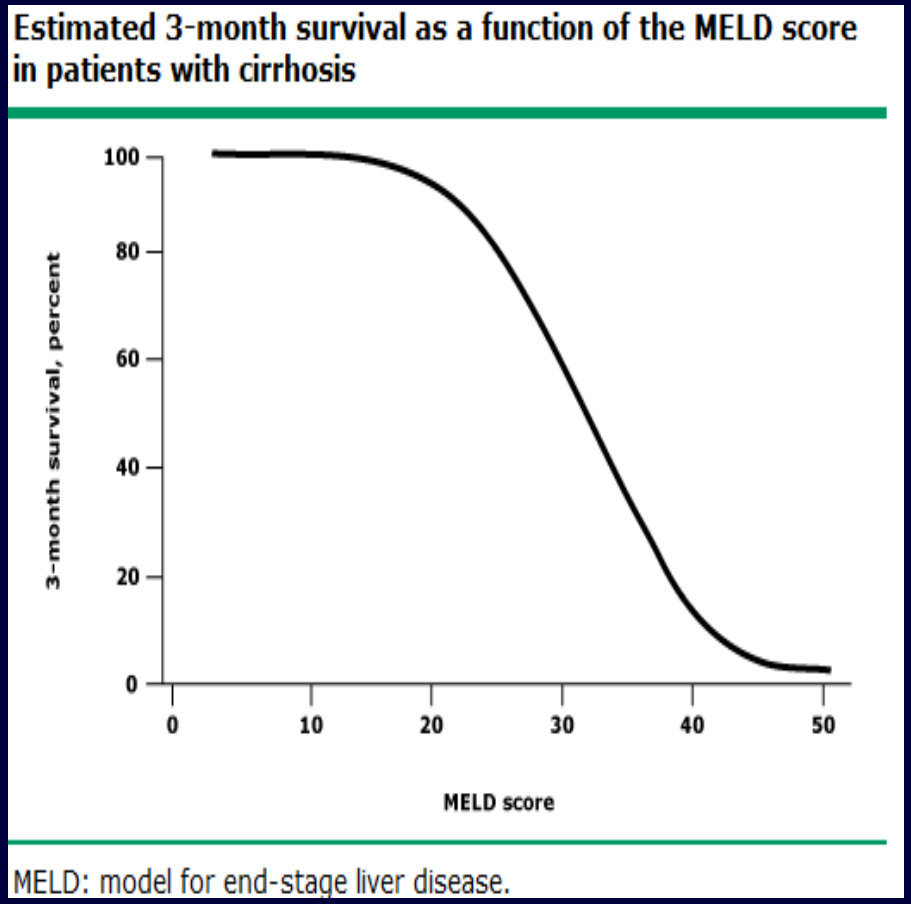
APPROPRIATE PATIENT SELECTION AS A KEY TO INCREASE THE BENEFIT/RISK RATIO FOR ELAD

Ram Subramanian M.D.
Hepatology and Critical Care
Emory University School of Medicine
Atlanta, USA

OUTLINE

- Review the prognostic utility of the MELD score in liver disease and failure
- Examine survival analysis results in the VTI-208 ELAD study, and discuss implications of findings regarding high MELD pts
- Describe the complex multi-organ system derangements in high MELD patients that pose challenges to ELAD administration
- Outline the potential benefits and risks of ELAD therapy in the context of current ICU management

PROGNOSTIC UTILITY OF MELD SCORE IN CIRRHOSIS



Wiesner et al. Gastro 2003

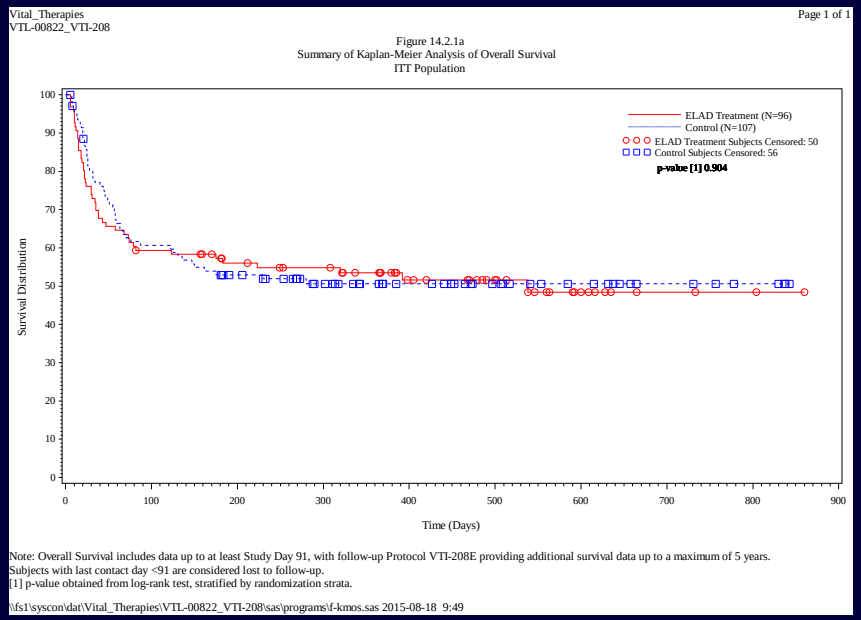
MELD : f (INR, Bili, Cr)

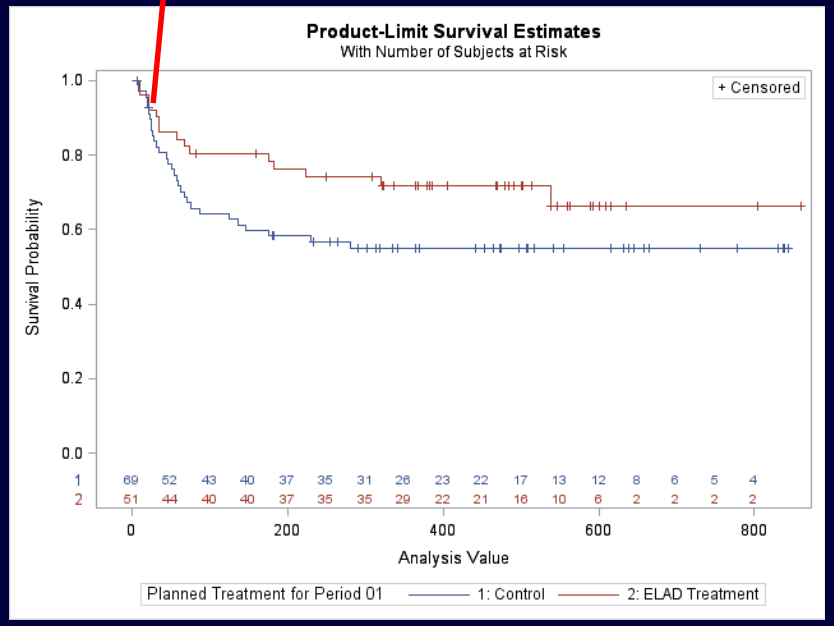
APPLICATIONS OF MELD RELATED PROGNOSIS

- Cirrhosis: Higher MELD patients associated with:
  - Higher risk of variceal bleeding (*Amitrano et al. J. of Hep 2005*)
  - Higher risk of infections (*Alessandria et al. Hepatology 2005*)
  - Higher risk of AKI (*Moreau et al. Gastro 2013)*
  - Higher ICU mortality (*Karvellas et al. Crit Care Med 2010*)
- Alcoholic Hepatitis: MELD more accurate predictor of mortality than Maddrey score (*Dunn et al. Hepatology 2005*)
- Acute Liver Failure: MELD independent predictor of mortality in non-APAP ALF (*Kremers et al. Hepatology 2004*)

Survival Curves in VTI-208 study:
Any survival benefit of ELAD in severe AAH ?

Curves split only after 20 days, suggesting delayed mechanism of ELAD benefit, and need for early aggressive CCM management

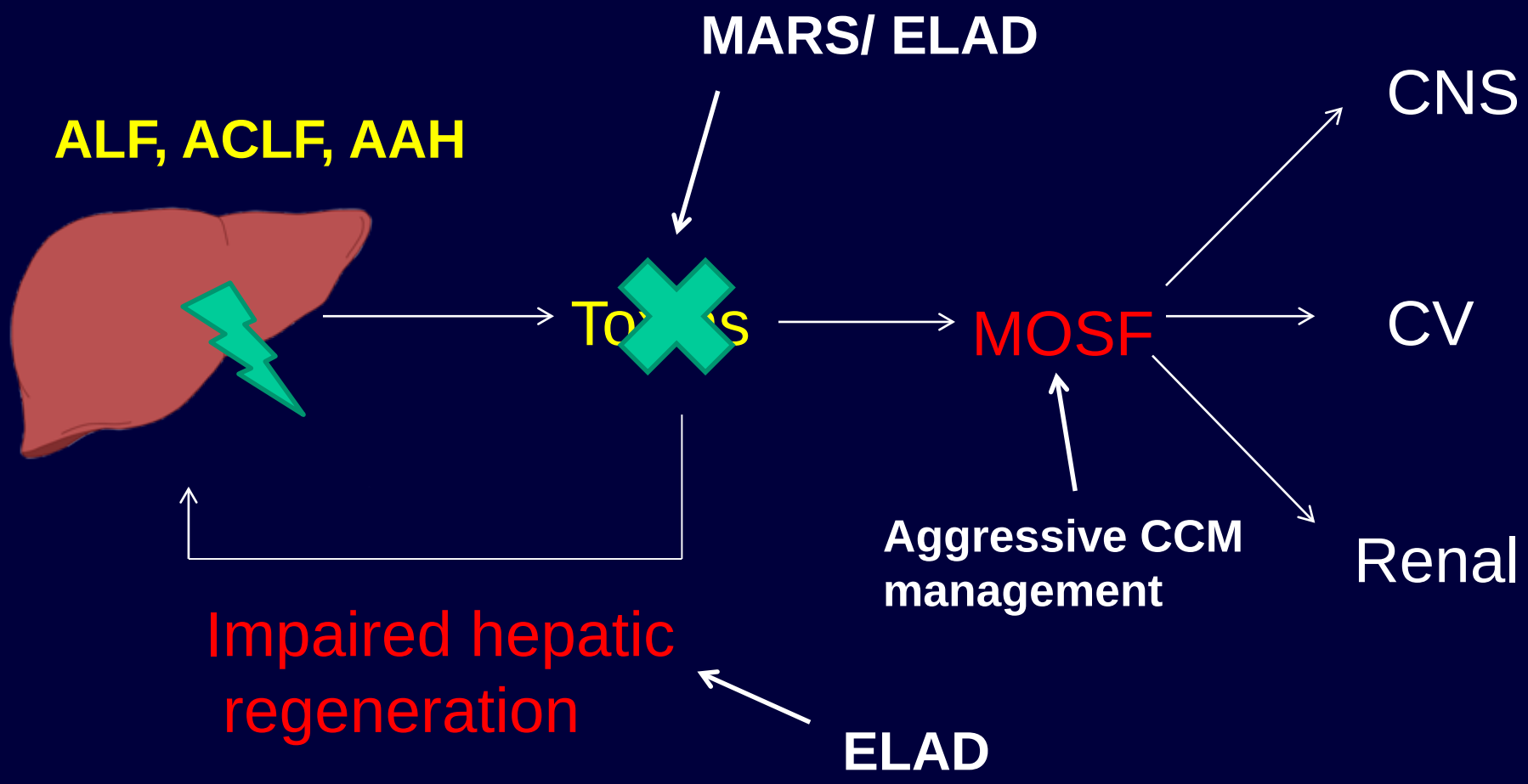




n= 203, MELD 18-35
HR=1.027, log rank 0.9

n= 120, MELD < 28
HR = 0.58, log rank 0.077

Schematic for Liver Support in the High MELD patient

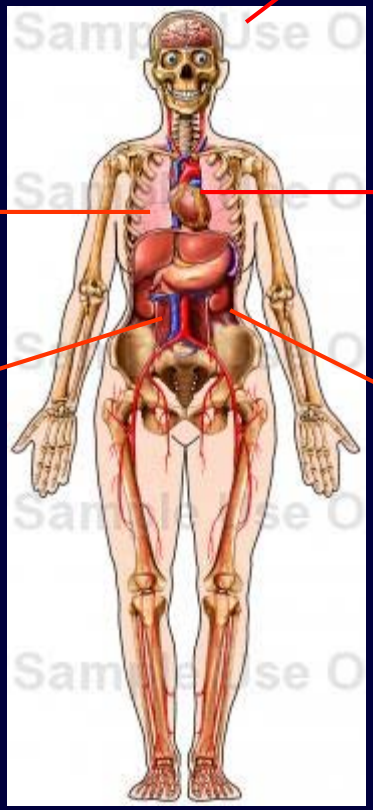


Management Challenges in High MELD Patients Related to ELAD

Multi-Organ Dysfunction in Liver Failure

Hepatic Encephalopathy

Acute Lung Injury



Distributive Shock

Portal HTN:
- Variceal bleeding
- Ascites/ SBP

Acute Kidney Injury

- *Coagulopathy*
- *Metabolic Acidosis*
- *Immunocompromised state: infectious complications*

Hepatic Encephalopathy (HE)

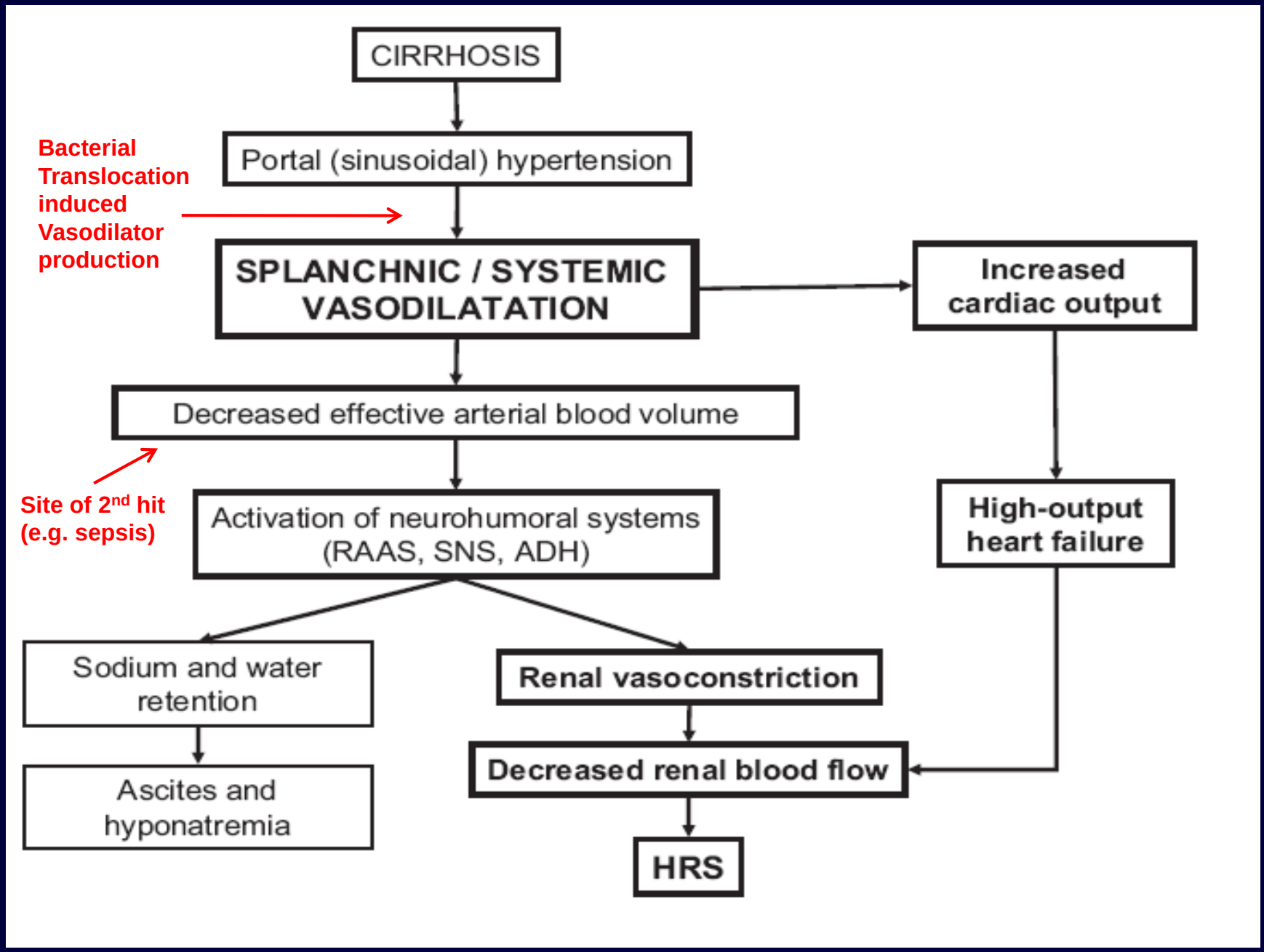
- Can progress to severe HE refractory to maximal medical therapy and requiring intubation for airway protection

- Candidate toxins: ammonia, endogenous benzodiazepines, cytokines related to septic encephalopathy

- Role for MARS: Multiple studies, including RCT (*Hassenein et al. Hepatology 2007*) have demonstrated improvement in HE in ALF, ACLF and AAH. Potential mechanisms: removal of ammonia and albumin bound endogenous benzodiazepines

- Ammonia elimination and ELAD? : Some findings suggest that urea synthesis in C3A cells occurs independent of the urea cycle (via arginase II pathway), and therefore, does not provide ammonia elimination (*Mavri-Damelin et al. Biotech & Bioeng. 2008*)

Hemodynamic Derangements in Cirrhosis



HEMODYNAMIC CHALLENGES (1)

- Baseline abnormal cirrhotic hemodynamics characterized by low MAP mediated by splanchnic and peripheral vasodilation (*How should hypotension/ shock be defined ?)*

- Assessment of fluid/ intravascular status challenging in the critically ill cirrhotic
  - Static indices of preload (e.g. CVP , PCWP) inadequate, especially in the setting of mechanical ventilation and tense ascites
  - Utilization of pulse contour analysis based devices (e.g. Lidco, Vigileo) and Echocardiography should be considered.

- Utility of lactate and central venous saturation in guiding fluid and vasoactive agent therapy compromised by abnormal pre-shock values.

- Minimal insults in vascular tone/ volume due to septic/ hypovolemic insults can result in hypotension/ shock, and decreased perfusion to end organs and extracorporeal circuit.

HEMODYNAMIC CHALLENGES (2)

- Evidence of abnormal myocardial function (cirrhotic cardiomyopathy), characterized by systolic & diastolic dysfunction, and impaired b-adrenergic receptor function

- In the setting of tense ascites, cardiac preload can be compromised by IVC compression due to abdominal compartment syndrome; role for therapeutic paracentesis.

- Evidence for high incidence of adrenal insufficiency in septic shock in the setting of cirrhosis (*Tsai et al. Hepatology 2006*). Role for stress dose steroids in septic shock refractory to initial vasoactive agent support.

- ELAD study and vasoactive agent support:

  MELD < 28: ELAD arm: n=3 Control: n=7

  MELD ≥ 28: ELAD arm: **n= 15** Control: **n= 13**

PULMONARY CHALLENGES

- Immunocompromised state risk factor for both intra-thoracic and extra-thoracic infection triggered ARDS (*Bajaj et al. Hepatology 2012*) . Increased mortality of ARDS in setting of cirrhosis (*Monchi et al. 1998*)

- Evidence supportive of decreased alveolar macrophage and T cell activity in alcoholic cirrhotics (*Wallaert et al. Am Rev Rep Dis 1991*)

- The negative effect of positive pressure ventilation on venous return can have profound deleterious effects on hemodynamic status; rationale for low TV strategy

- ELAD study:
  - Mechanical Ventilation:
    MELD < 28: ELAD arm: n=5 Control: n=1
    MELD ≥ 28: ELAD arm: n= 3 Control: n=2

  - ARDS: ELAD: n=6 Control: n=4 - PNA: ELAD : 15 C: 16

RENAL CHALLENGES

- Tenuous baseline cirrhotic hemodynamics predisposes to development of AKI in the setting of *minimal* cardiovascular insults (*implications for extracorporeal therapy in high MELD patients?*)

- Recent multi-center European study identified AKI as most common extrahepatic injury in ACLF and major contributor to mortality (*Moreau et al. Gastro 2013*)

- Infection, and in particular SBP, classic trigger for T1 HRS (*Follo et al. Hepatology 1994*)

- Renal dysfunction can compromise platelet qualitative function; role of DDAVP

- Concomitant AKI in the setting of liver failure can cause a rapidly progressive anion gap metabolic acidosis, necessitating consideration for early CRRT. *No evidence yet for lactate clearance acutely by ELAD*

HEMATOLOGIC CHALLENGES (1)

- Given the depletion of both procoagulant and anticoagulant proteins, the net state of coagulopathy is unpredictable

- Conventional measures of coagulation (e.g. INR, PT) not applicable; *role for TEG ?*

- The presence of infection and sepsis can trigger:
  - a prothrombotic cascade in the microcirculation
  - an anti-thrombotic pathway via increase in endogenous heparinoids (*Montalto et al, J Hep. 2002*)
  - DIC mediated worsening in baseline thrombocytopenia

- Co-existing renal dysfunction can compromise platelet qualitative function; role of DDAVP

Hematologic Issues Related to Liver Support

- Heparin use may influence measures of coagulation in subject, thereby affecting potential study end points related to liver support

- Titration of heparin challenging, since measures of anticoagulation (e.g. PTT, anti Factor Xa) may be inaccurate due to antithrombin deficiency (*Bechmann et al. Liver Int 2011*)

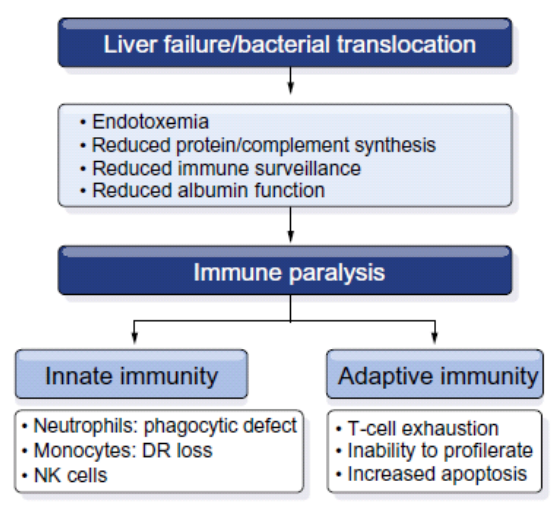
- Risk of worsening thrombocytopenia and hemolytic anemia

- Presence of infection can generate endogenous heparinoid production that can have an additive effect on exogenous heparin anticoagulation

- Regional citrate anticoagulation not compatible with ELAD, thereby necessitating low dose heparin (~ 300 U/hr)
- ELAD trial hematologic side effects:
  - Anemia: E = 48% C=17.5%
  - Thrombocytopenia: E= 37% C=11%
  - Coagulopathy: E=32.6% C=12%
  - -DIC: E=9.5% C= 1%

INFECTIOUS DISEASE ISSUES

- The patient with decompensated liver disease is an immunocompromised host, and at risk for bacterial, fungal and viral infections



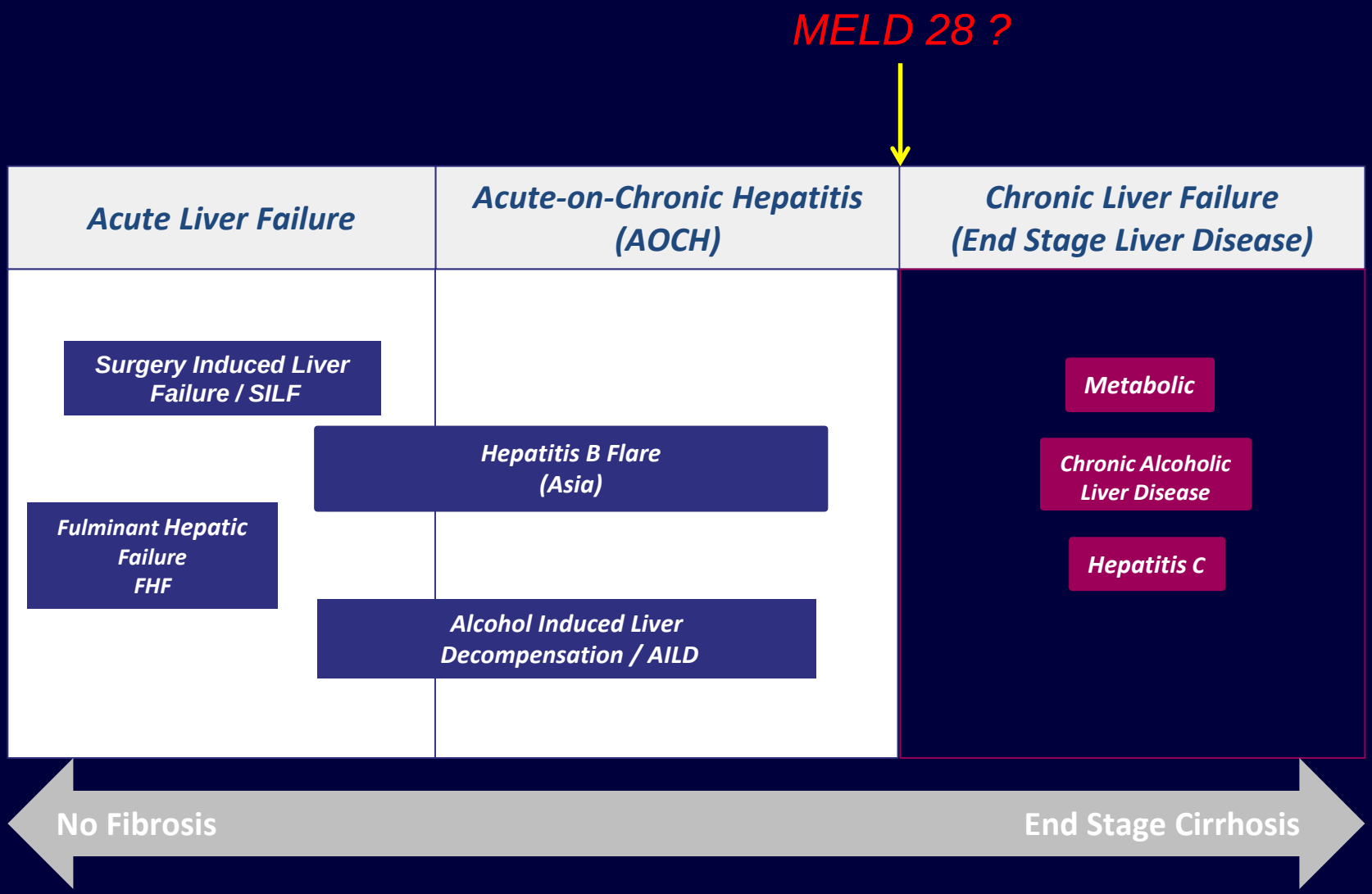
Jalan. J of Hep. 2012

- Higher MELD patients associated with increased risk of infections (*Alessandria et al. Hepatology 2005*)

- Nosocomial infections independent risk for mortality due to MOSF in hospitalized cirrhotic patients (*Bajaj et al. Hepatology 2012*); common infectious sources include UTI, pneumonia, SBP, cellulitis and *line infections*

- ELAD trial: *Bacteremia:* E= 18% C= 8.3%

The Application of ELAD



SUMMARY

- The application of extracorporeal liver support in the high MELD patient is challenging, and therefore, appropriate patient selection with respect to hepatic disease severity is crucial.

- Early and aggressive intensive care support of multi-organ dysfunction is crucial in improving survival.

- In addition, early appropriate ICU care appears to be essential in creating a ‘window of stability’ for co-administration of bioartificial liver support with ELAD.

- Future paradigms of extracorporeal liver support in a critical care setting may include a combination of devices, including hemodialysis, albumin dialysis and bioartificial liver support.