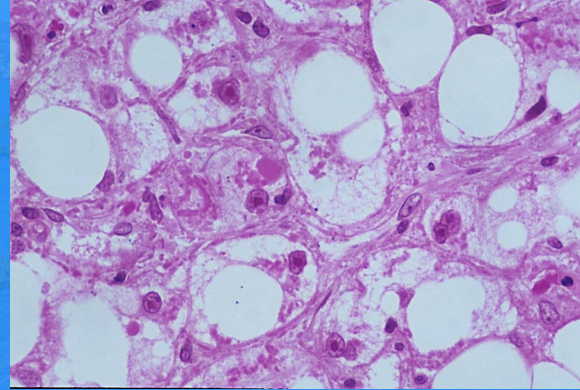
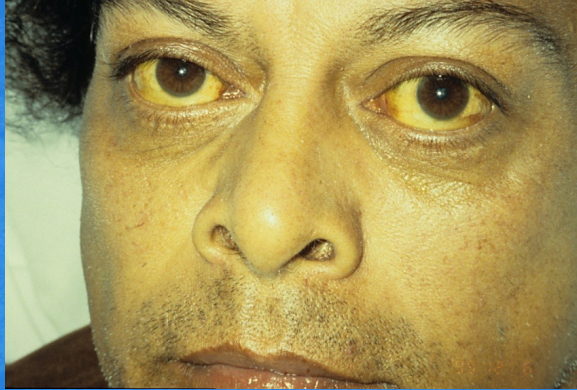




2023 SCSSG
LIVER SYMPOSIUM
DECEMBER 9-10, 2023

Alcohol-Associated Hepatitis



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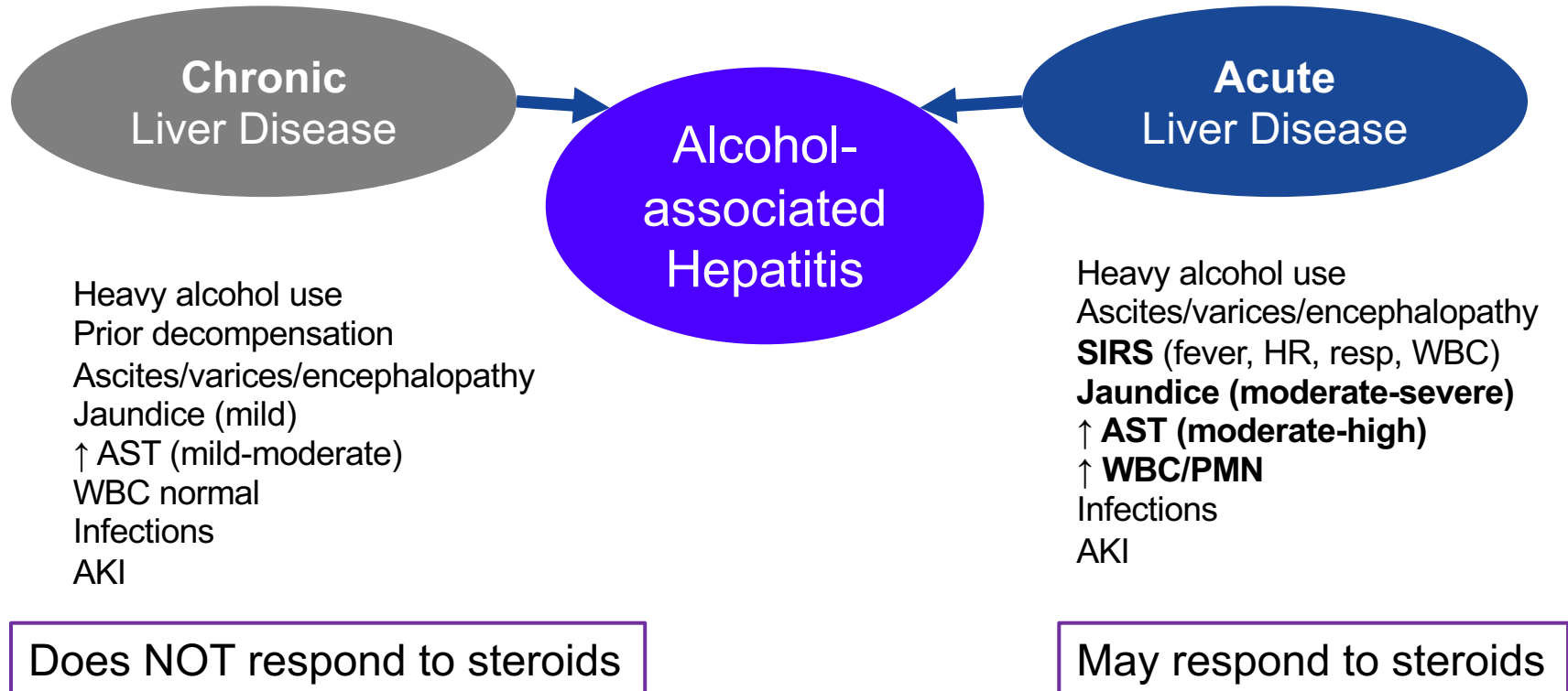
Disclosures / Conflict of Interest

- Speaker's Bureau: none
- Honoraria: none
- Clinical Trials: none
- The opinions and recommendations do not represent the views of the Department of Veterans Affairs.
- I will discuss non-FDA approved medications to treat AH

Outline

- Diagnosis
- Evaluation
- Severity scoring systems (DF, MELD)
- Corticosteroids?
- Lille Score
- Infections
- Abstinence
- Liver transplantation

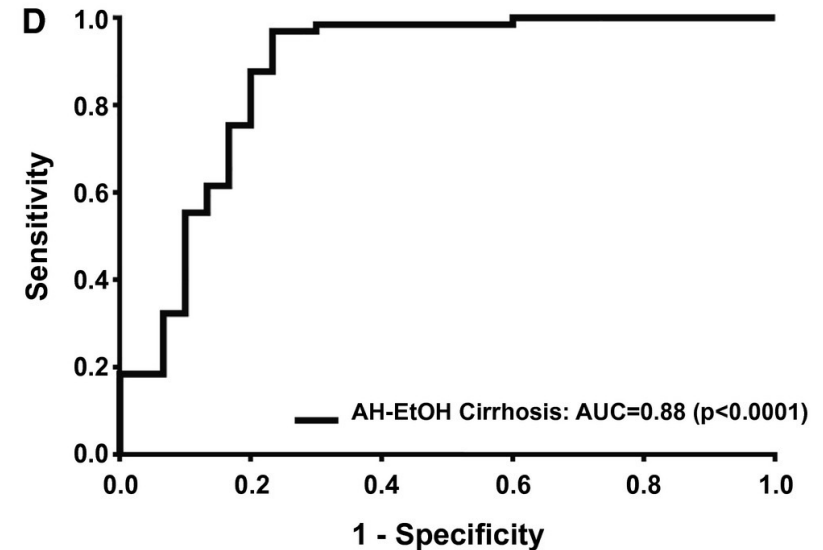
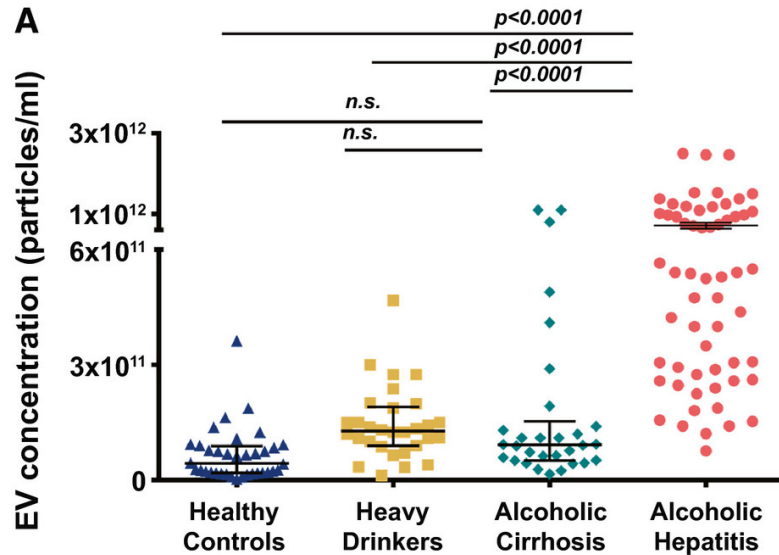
AH Is a Combination of Acute and Chronic Injury



Clinical Definition of Alcohol-Associated Hepatitis

- Clinical history (i.e., risk for liver disease):
 - Heavy drinking for > 6 mos (> 40 g/d for women and 60 g/d for men)
 - Onset of jaundice while still drinking (abstinent < 60 days)
- Lab features (i.e., presence of liver injury):
 - Bilirubin > 3.0 mg/dL
 - AST > 50, but < 400;
 - ALT < 200
 - AST/ALT ratio > 1.5,
- Features of Systemic Inflammatory Response Syndrome (SIRS) are common
- Liver biopsy for confirmation in patients with confounding factors

Blood Test (Research): Extracellular Vesicles



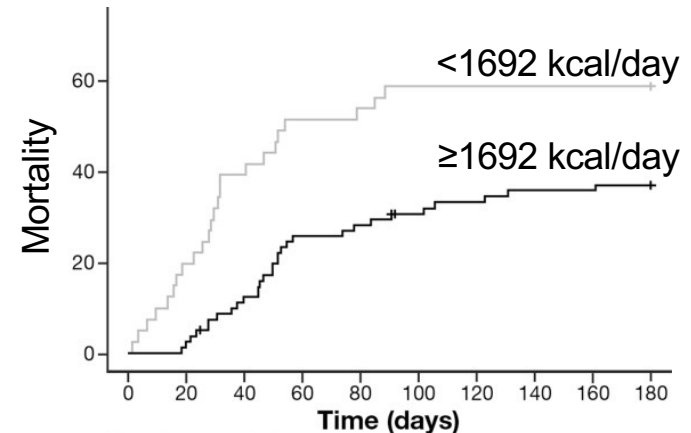
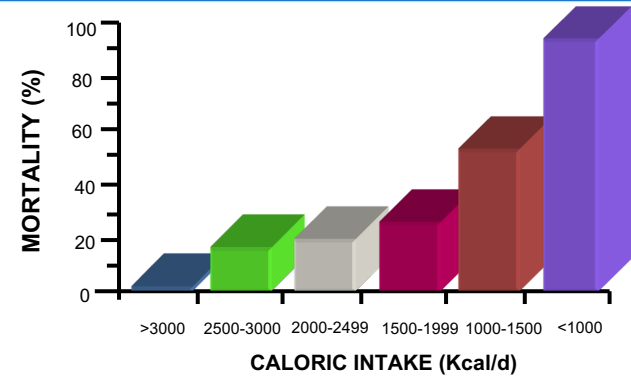
General Treatment of Alcohol-Associated Hepatitis

- Hospitalize patients with $DF \geq 32$
- Infection
 - Culture ascites, urine, blood; CXR
 - if diarrhea, test stool for *C. diff.*
- Ultrasound of abdomen
 - Ascites
 - Bile ducts (exclude obstruction)
 - Masses in liver (exclude abscess, tumor)
 - Portal vein and hepatic veins (exclude obstruction)

Treatment of Alcoholic Hepatitis

Nutrition

- Diet (per kg ideal body weight)
 - 35–40 cal/kg/d (80 kg = 2,600 to 3,200 Cal)
 - 1.2–1.5 gram protein/kg/d
 - 2 gram sodium
 - 4–5 meals per day
 - Oral (if anorexia then NG feeding tube)
- Multivitamins and minerals
 - Thiamine, B6, B12, folate, zinc, selenium



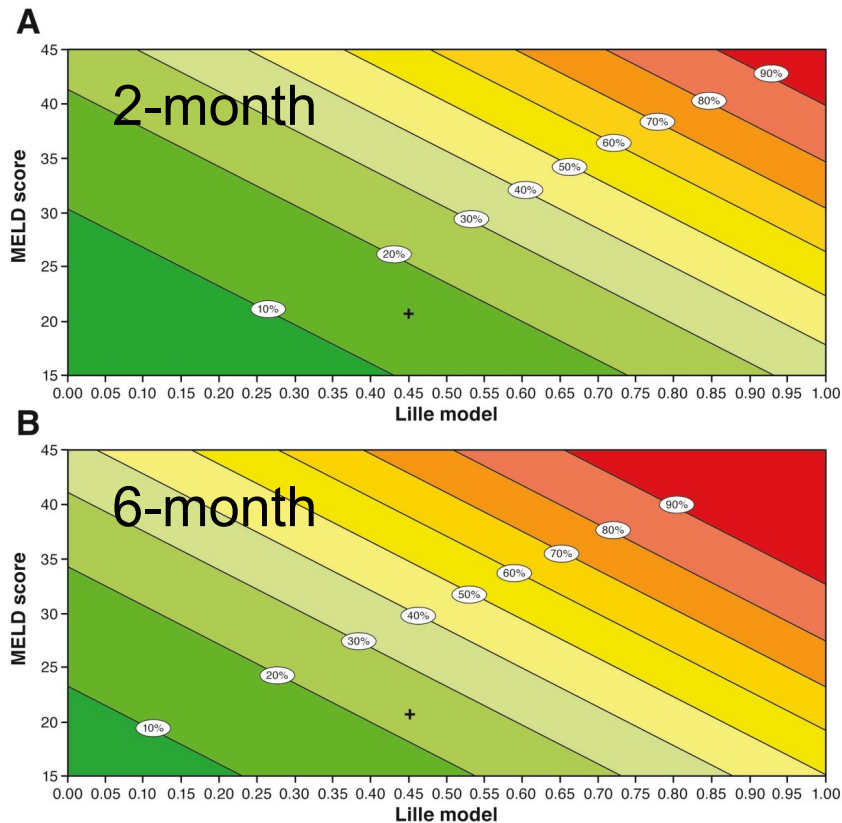
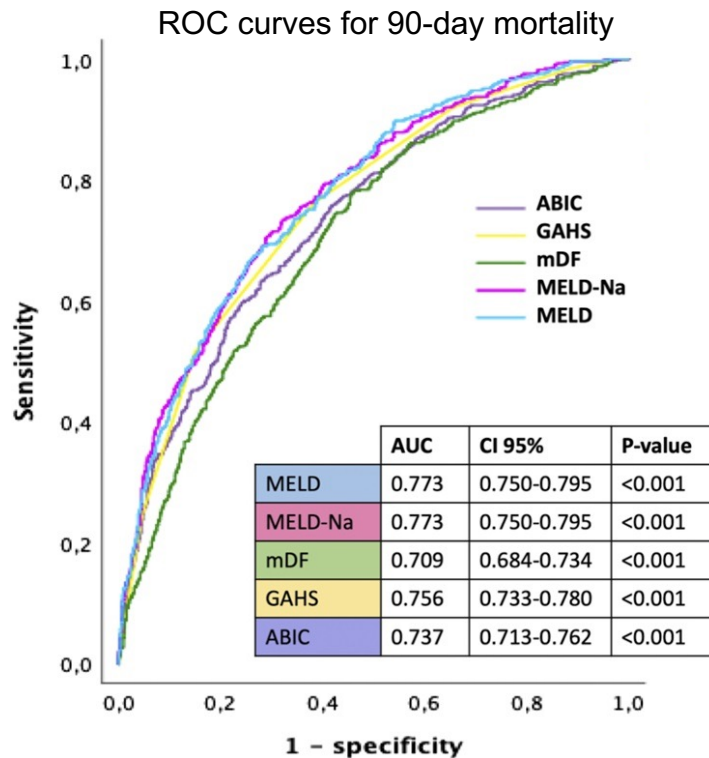
Scoring Systems and Treatment

| | Bilirubin | PT or INR | Creatinine or Urea | Age | WBC | Albumin | ECB | Cut-off |
|--------------|-----------|-----------|--------------------|-----|-----|---------|-----|---------|
| Maddrey's DF | ✓ | ✓ | | | | | | ≥32 |
| MELD | ✓ | ✓ | ✓ | | | | | ≥20 |
| ABIC | ✓ | ✓ | ✓ | ✓ | | | | >6.7 |
| GAHS | ✓ | ✓ | ✓ | ✓ | ✓ | | | >8 |
| Lille Model | ✓ | ✓ | ✓ | ✓ | | ✓ | ✓ | <0.45 |

PT=protime; INR= international normalized ratio; WBC=white blood cell; ECB=early change in bilirubin (1 week).

Maddrey's discriminant function (DF): Maddrey. *Gastroenterology*. 75;1978; Model for End Stage Liver Disease (MELD): Srkiureja. *J. Hep.* 42; 2005; Age, Bilirubin, INR, Creatinine (ABIC): Dominguez. *Am J Gastro.* 103;2008; Glasgow Alcoholic Hepatitis Scale (GAHS): Forrest. *Gut.* 24;2005 & 56;2007; Lille Model: Louvet. *Hepatology*. 45;2007.

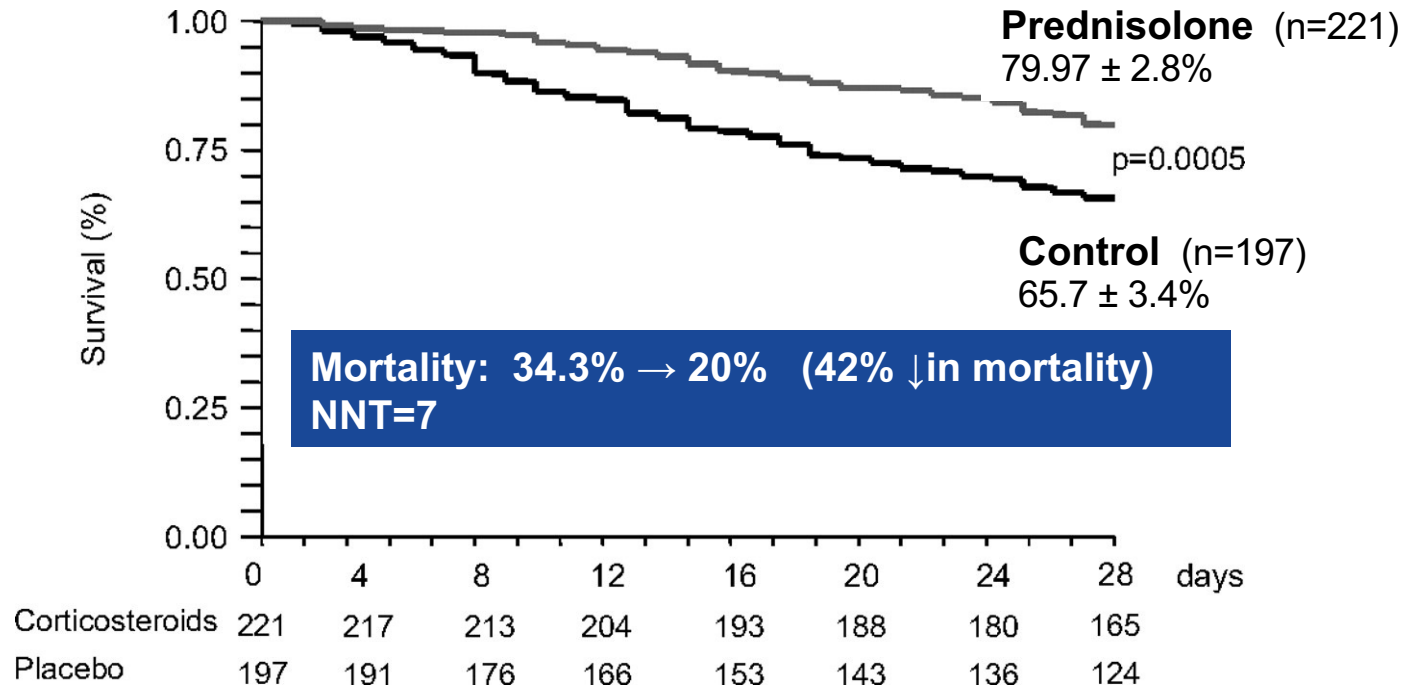
Predicting Mortality



Alcohol-Associated Hepatitis: Corticosteroids

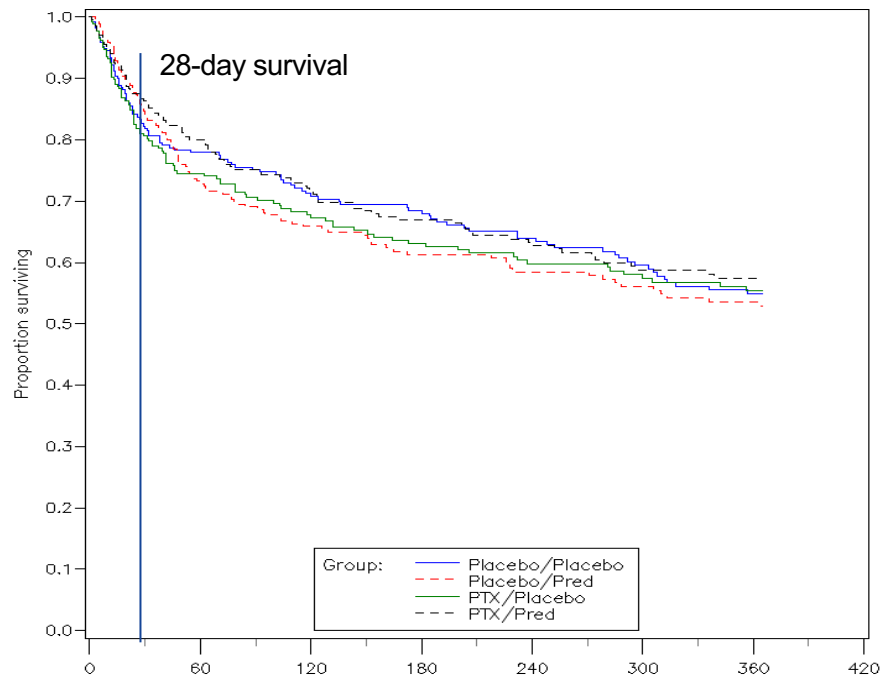
- Prednisone 40 mg/day for 28 days
- Prednisolone 40 mg/day for 28 days
- Methylprednisolone 32 mg/day for 28 days

28-Day Survival With Prednisolone vs. Control, DF≥32 Meta-Analysis of Individual Data From 5 RCTs*



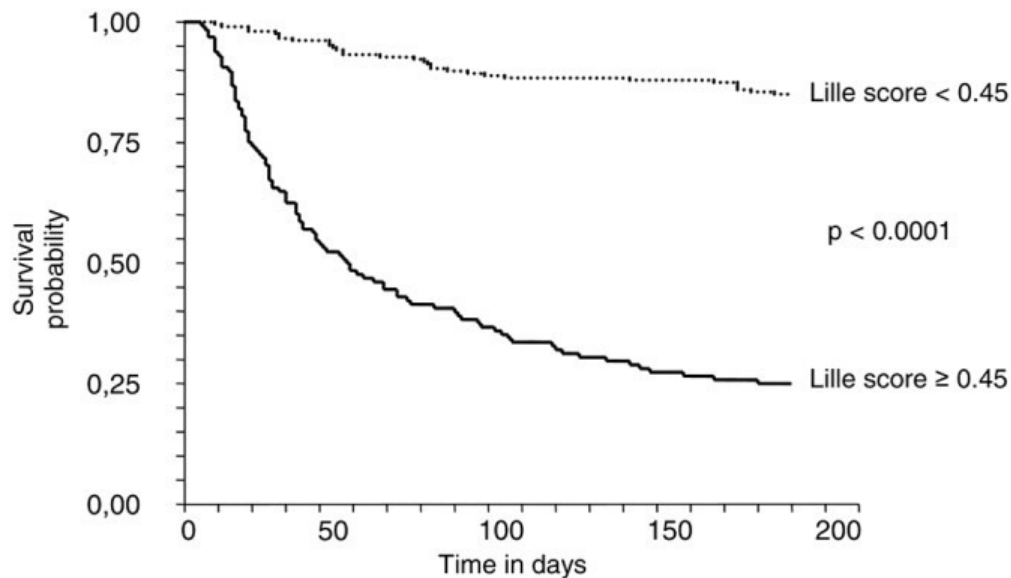
* Mendenhall. 1984; Ramond. 1992; Carithers. 1989; Cabre. 2000; Phillips. 2006; Mathurin. *Gut*. 2011;60:255-260.

STOPAH: Kaplan-Meier Survival, 1-Year



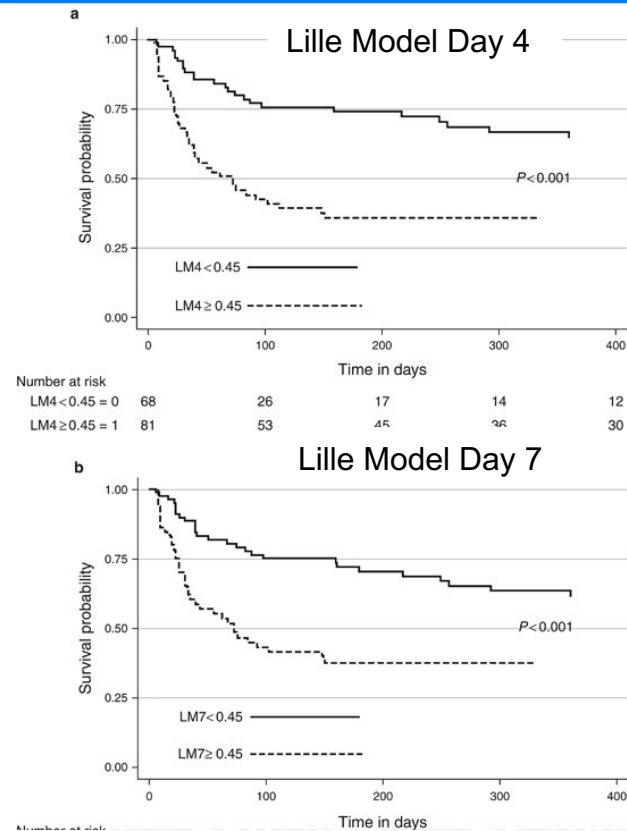
| | | 60 | 120 | 180 | 240 | 300 | 360 |
|------------------|-----|-----|-----|-----|-----|-----|-----|
| Patients at Risk | | | | | | | |
| Placebo/Placebo | 272 | 199 | 159 | 142 | 121 | 104 | 89 |
| Placebo/Pred | 274 | 182 | 139 | 116 | 102 | 91 | 84 |
| PTX/Placebo | 271 | 178 | 133 | 119 | 104 | 95 | 83 |
| PTX/Pred | 272 | 201 | 157 | 137 | 115 | 101 | 84 |

Stopping Corticosteroids: Lille Score



Age, creatinine, bilirubin, protime, and albumin on Day 0 with change in bilirubin on Day 7 to evaluate response to treatment with corticosteroids (www.lillemodel.com)

Louvet et al. *Hepatology*. 2007;45:1348; Garcia-Saenz et al. *Am J Gastro*. 2017;112:306.



Infection in Alcoholic Hepatitis

Infection *prior* to starting steroids

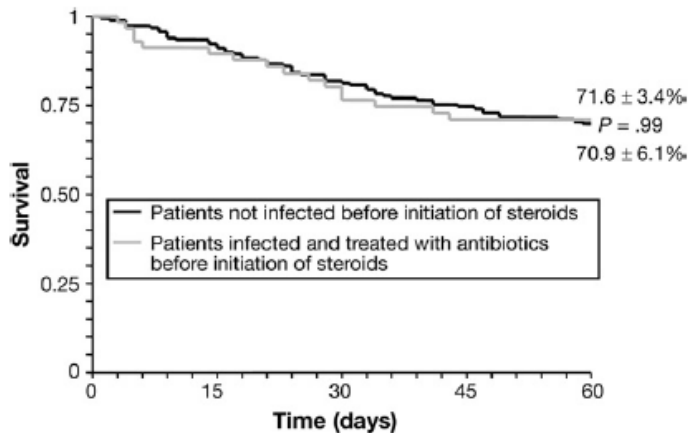


Figure 1. Survival impact of infection diagnosed before initiation of corticosteroids.

Infection *after* starting steroids

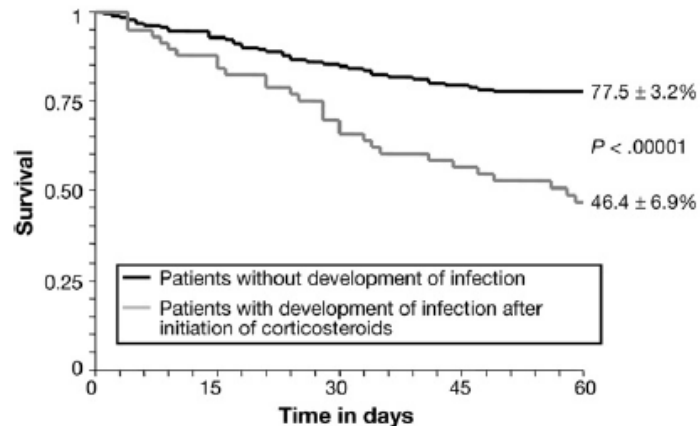
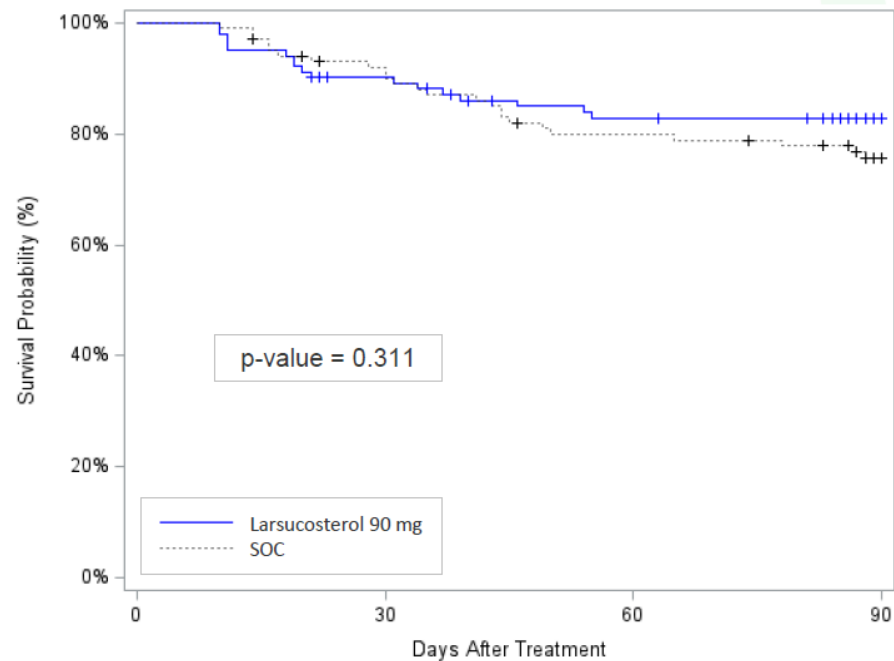
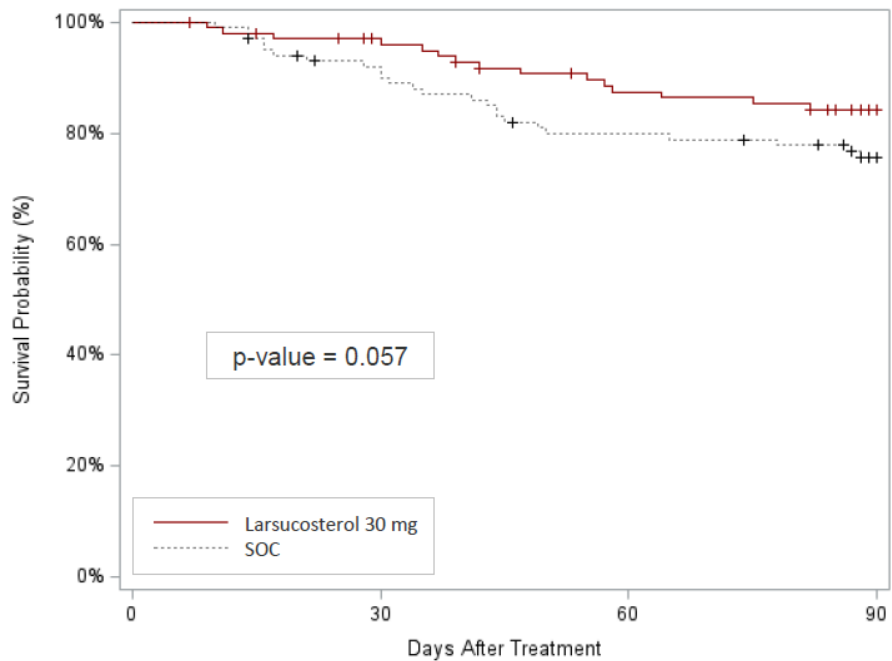
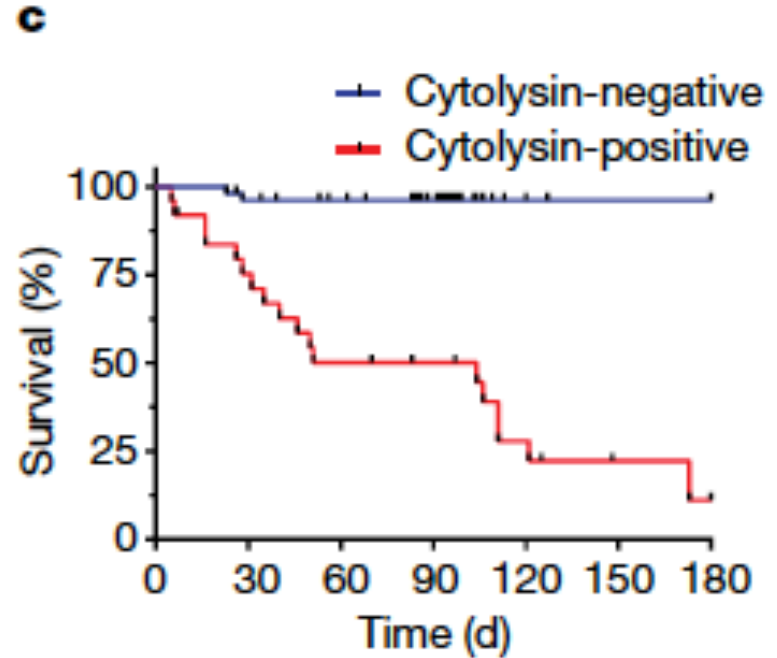
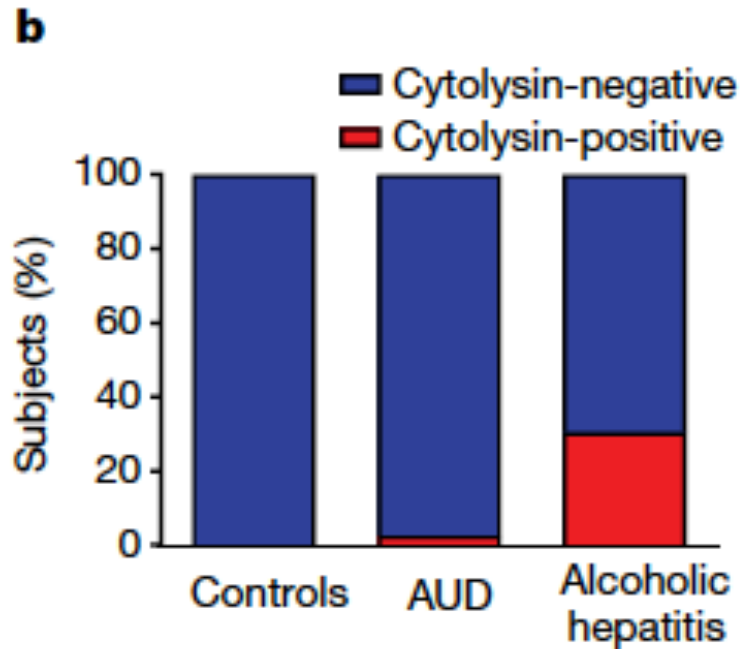


Figure 2. Two-month survival according to the development of infection after corticosteroids.

Larsucosterol: 90-Day Survival (Kaplan-Meier)



Stool *Enterococcus faecalis* Cytolysin-Positive Species Is Associated With Poor Survival in AH



AH: Two Organs, Two Diseases, Two Disciplines



Liver
Disease

Alcoholic
Hepatitis

Substance
Use Disorder



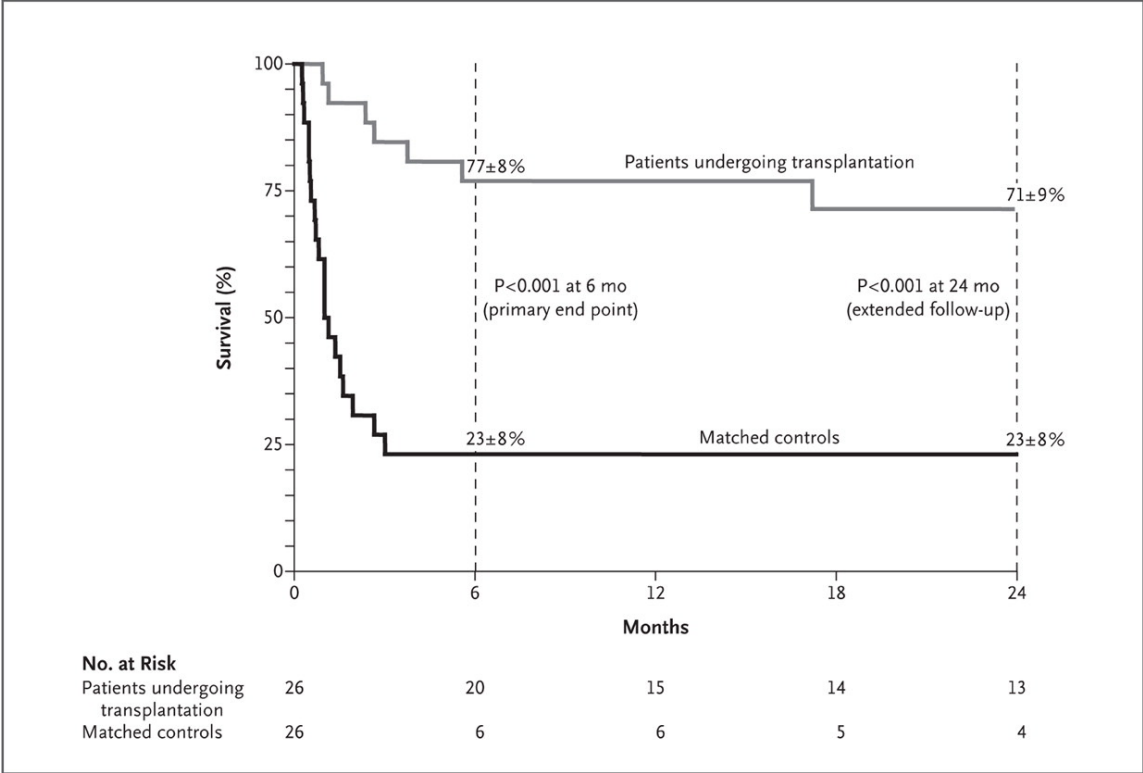
Primary reason for hospitalization
HE/infections/bleeding/renal
Predicts 6-month mortality
Gastroenterologist
Clinical course somewhat predictable

Outpatient management
Family/relationships/work/finances
Predicts mortality after 6-month
Mental health provider
Clinical course unpredictable

Abstinence and 1-Year Mortality

| Alcohol consumption at Day 90 | Odds Ratio for 1-year mortality | | | |
|--|---------------------------------|-------------|-------------------------|---------|
| | n | Odds ratio | 95% Confidence Interval | p-value |
| Abstinent | 321 | 1.0 | | |
| Not reduced | 50 | 2.99 | 1.47–6.05 | <0.001 |
| Reduced but above safety limits | 48 | 2.28 | 1.07–4.86 | 0.032 |
| Reduced to below safety limits | 59 | 2.17 | 1.07–4.39 | 0.031 |

Early Liver Transplantation (i.e., < 6 Months Abstinance) for Severe Alcoholic Hepatitis



Mathurin P et al. *NEJM*. 2011; 365:1790-1800.

Early Liver Transplantation for Severe AH: A Prospective Study

Patient Survival (2 year)

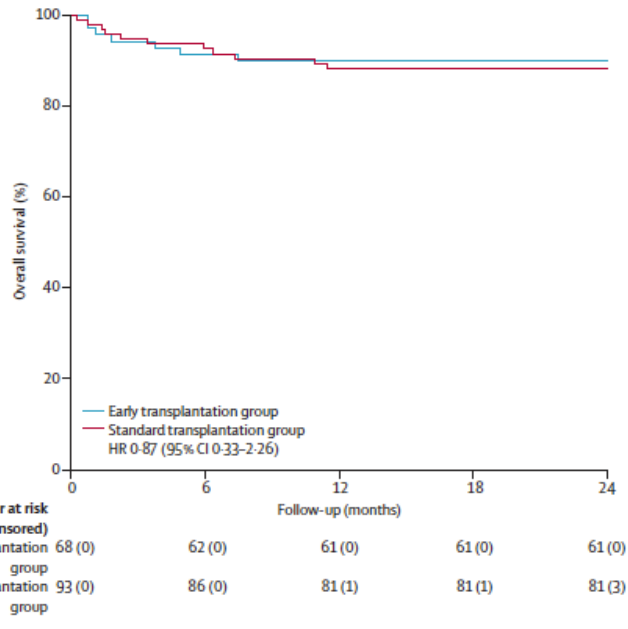


Figure 3: 2-year overall survival after liver transplantation in the early liver transplantation group compared with the standard transplantation group in the QuickTrans study

Alcohol Use (2 year)

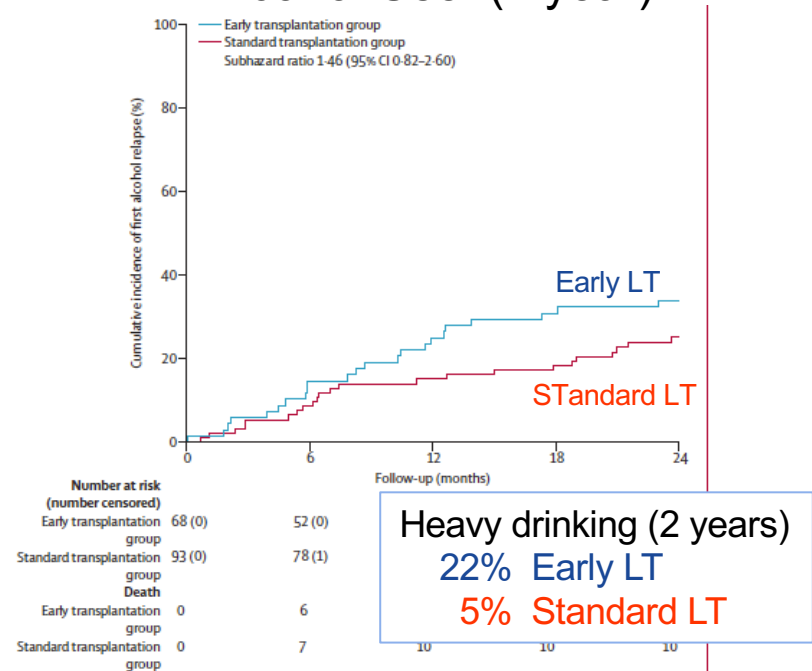
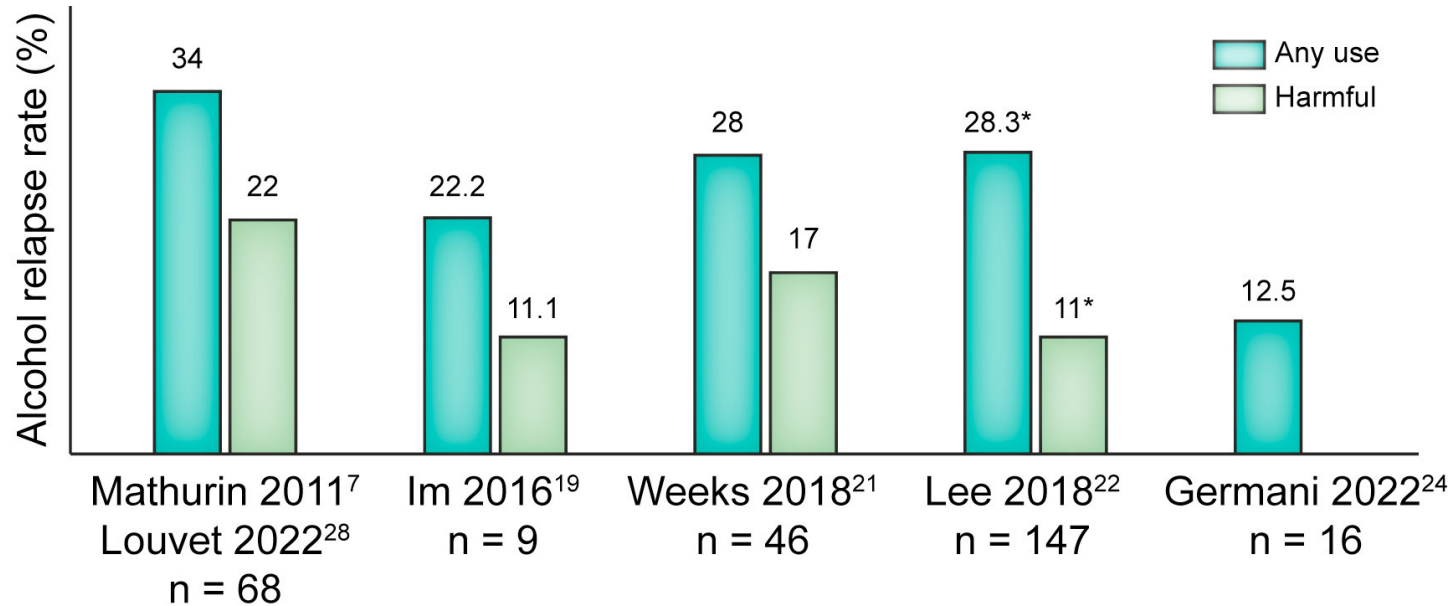


Figure 2: 2-year cumulative incidence of first alcohol relapse after liver transplantation in the early transplantation group and standard transplantation group enrolled in the QuickTrans study

Alcohol Use After Early Liver Transplantation for Alcohol-Related Hepatitis (~2–3 Years)



Predicting Alcohol Use After Liver Transplantation

Sustained alcohol use post-LT (SALT)

| Variable | Points |
|--|--------|
| >10 drinks/day at presentation | +4 |
| ≥2 failed rehabilitation attempts | +4 |
| Prior alcohol-related legal issues | +2 |
| Non-THC illicit substance abuse | +1 |
| ≥5 pts predicted sustained alcohol use post-LT | |

Psychosocial Model

Failure to engage in an intensive outpatient program
 Relapse after an initial attempt at sobriety
 Ongoing alcohol consumption after liver disease Dx

High-risk alcoholism relapse (HRAR)

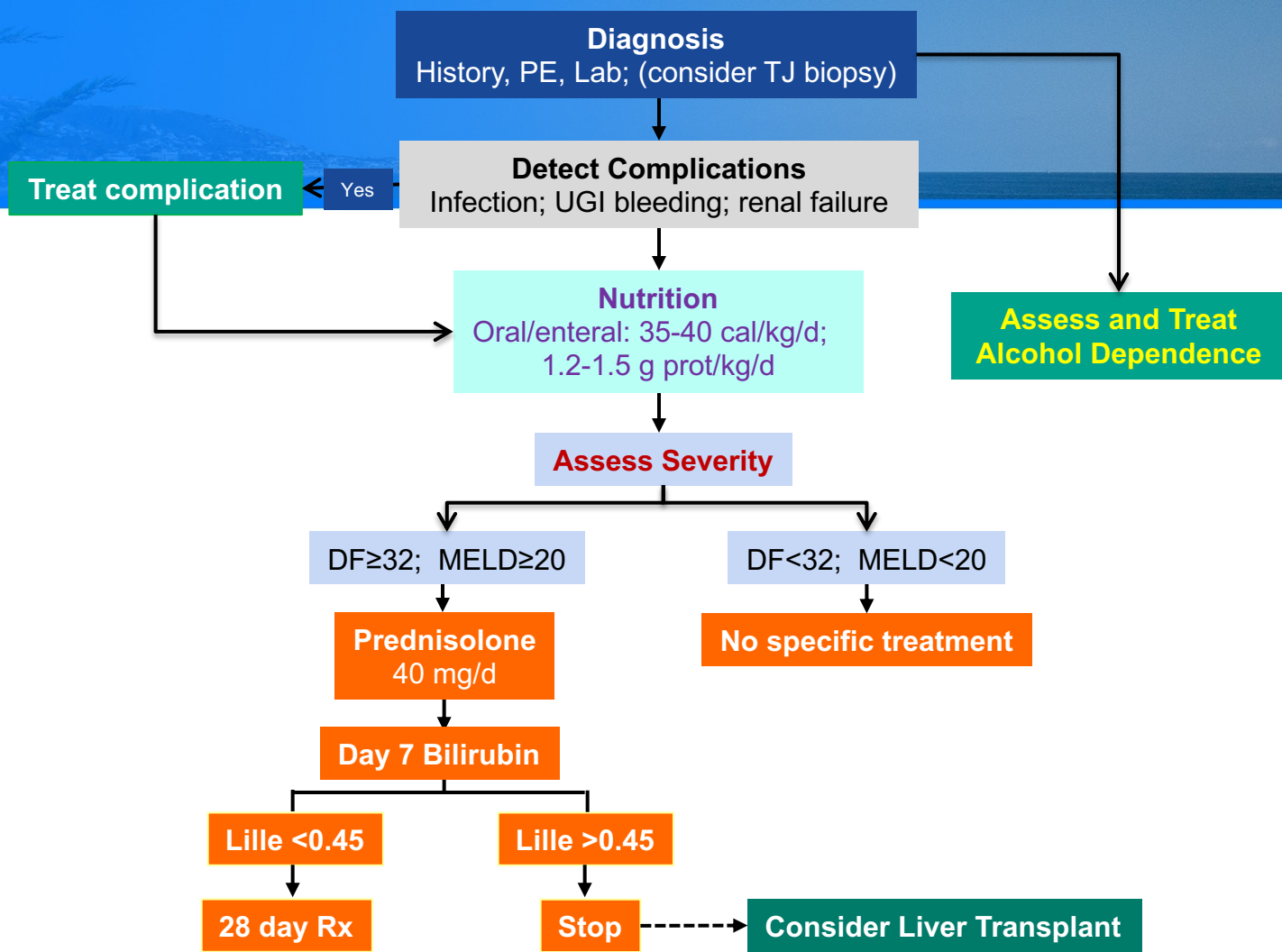
| Variable | 0 | 1 | 2 |
|---------------------------|-----|-------|-----|
| Duration (y) | ≤11 | 11-25 | ≥25 |
| Drinks/day | ≤9 | 9-17 | >17 |
| Prior Inpatient Tx | 0 | 1 | ≥2 |
| Low (0-3) High (4-6) | | | |

Stanford Integrated Psychosocial Assessment for Transplantation (SIPAT)

Readiness level and illness management (5 items)
 Support system level of readiness (3 items)
 Psychological stability and psychopathology (5 items)
 >40 suggests high psychosocial risk post-transplant

Alcohol-Associated Hepatitis: Summary

- Nutrition is important
- Discriminant Function (DF) or MELD to assess corticosteroids
- Steroids *probably* decrease mortality 30% in 1 month
- No survival benefit at 6 months
- Stop prednisolone if Lille score >0.45
- Infection surveillance before, during, and after steroids.
 - Steroids can be used after infection controlled
- Abstinence essential for long-term survival (referral)
- Consider liver transplant
 - No prior alcohol-related problems
 - Good insight and family support



48 Yo Man With Long History of Alcohol Use

- No prior hospitalizations for alcohol-related problems

| | 1 | 2 | 3 | 4 | | | |
|------------|-----|-----|-----|-----|-----|-----|-----|
| Bilirubin | 4.5 | 4.5 | 9.0 | 9.0 | 15 | 15 | 18 |
| AST | 66 | 120 | 88 | 120 | 88 | 130 | 130 |
| ALT | 38 | 66 | 52 | 66 | 52 | 77 | 77 |
| Albumin | 3.2 | 2.9 | 2.8 | 2.8 | 2.7 | 2.7 | 2.7 |
| Creatinine | 0.8 | 0.8 | 0.8 | 0.8 | 0.9 | 0.9 | 0.9 |
| WBC | 5.4 | 8.4 | 5.4 | 8.5 | 9.5 | 9.5 | 10 |
| INR | 1.3 | 1.3 | 1.3 | 1.3 | 1.3 | 1.3 | 1.3 |
| mDF | 18 | 18 | 23 | 23 | 29 | 29 | 32 |
| MELD-Na | 18 | 18 | 20 | 20 | 22 | 22 | 23 |
| AH? | | | | | | | |
| Rx? | | | | | | | |