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Alcoholic Hepatitis
(Teacher's Guide)

(30 minutes)

I. Objectives

- Recognize the signs and symptoms of alcoholic hepatitis
- Understand the treatment options and the limitations of the current data
- Recognize the appropriate patient to treat, and recall contraindications to treatment
- Recognize the poor prognosis of patients with severe alcoholic hepatitis

II. Case

A 28-year-old woman complains of severe right upper quadrant pain and jaundice. She has a low-grade temperature of 100.1^{o}F. On exam, she is icteric, but alert and oriented with no asterixis. She has a severely tender, enlarged liver. Her labs include: AST = 250 U/L, ALT = 112 U/L, total bilirubin = 25 mg/dL, alkaline phosphatase = 230 U/L, albumin = 3.0 g/L, creatinine = 1.4 mg/dL, WBC = 18,000/µL with a leftward shift, PT = 26 seconds and INR = 2.2.

What is your differential diagnosis for this patient?

Have members of the team generate a differential diagnosis for this patient, and list their suggestions on the board. Ask team members to offer support for or against their suggestions.

A reasonable differential would include: choledocholithiasis, cholangitis, spontaneous bacterial peritonitis, acute hepatitis (viral or toxic less likely given low levels of AST and ALT, unless patient is presenting very early), pancreatitis, appendicitis, or an infiltrative process in the liver resulting in capsular swelling.

What signs, symptoms and laboratory values would increase the likelihood of alcoholic hepatitis over other diagnoses on your list?

Signs, symptoms and lab values that can be seen in alcoholic hepatitis include:

- *Hepatomegaly*
- *Jaundice*
- *Right upper quadrant pain*
- *Fever and leukocytosis*
- *Encephalopathy*
- *Hepatic bruit*
- *AST/ALT ratio > 2 with total levels < 300*

What would be your next step in the case?

Have team members suggest how they would rule in or rule out items on their differential diagnosis. Are they comfortable enough with a single diagnosis at this point to initiate empiric treatment, or would they opt for further tests or empiric treatment of multiple diagnoses?

At a minimum, serologies for hepatitis A, B and C and a right upper quadrant ultrasound should be ordered. She should also be evaluated for a possible infection, given her fever and leukocytosis.

A liver biopsy is not usually necessary to establish a diagnosis of acute alcoholic hepatitis.

Case (cont.)

The ER admits her to you with a working diagnosis of choledocholithiasis. An ultrasound demonstrates a large liver but no gallstones or dilation of bile ducts, and minimal ascites. On exam, you hear a bruit over the right costal margin, and you note alcohol on her breath.

Would this patient benefit from corticosteroids? What about pentoxifylline?

Supportive treatment, including fluid and electrolyte replacement, nutritional support and monitoring for and treatment of alcohol withdrawal, should be given. The results of early studies of steroids to suppress inflammation in alcoholic hepatitis were mixed. Mild to moderate hepatitis often resolves with only abstinence. However, when steroid therapy was studied specifically in those with severe alcoholic hepatitis, evidence of a benefit began to emerge.

Review the modified Discriminant Function, which is used to define severity and predict prognosis in alcoholic hepatitis:[1-3]

DF = 4.6 x (prothrombin time – control time) + serum bilirubin (mg/dL)

Review the methods and results of the study by Carithers, et.al.[1] *The key finding of this trial was that in patients with severe alcoholic hepatitis, defined as a DF > 32 or*

hepatic encephalopathy, methylprednisolone significantly decreased short-term mortality, with a number needed to treat of 5.

Pentoxifylline is another agent that has been studied in severe alcoholic hepatitis. It inhibits tumor necrosis factor, which is found in excessive amounts in severe alcoholic hepatitis. Early studies of pentoxifylline showed promising results.

Now review the methods and results of the STOPAH study.[2] In this trial, prednisolone and pentoxifylline were given either alone or in combination to patients with a history of alcohol intake and a discriminant function of 32 or higher. Prednisolone demonstrated short-term (after adjustment for baseline prognostic factors) but not long-term reduction in mortality, Unlike previous small studies, this well-designed trial did not show any a mortality benefit of pentoxifylline compared to placebo in the short or long-term. Furthermore, the addition of pentoxifylline to prednisolone did not result in any further reduction in mortality.

Have the teams comment on the applicability of these therapies given the inclusion and exclusion criteria. In the STOPAH study, it is important to note that there was an increased rate of infection in the prednisolone group. Consensus statements support the use of steroids in properly selected patients (moderate to high severity of illness as defined by the Discriminant Function or the presence of hepatic encephalopathy, and the absence of exclusion criteria).[3]

Now calculate this patient's DF with the team. (Assume that the upper limit of a normal PT is 14.4 seconds.) Her DF is about 80. If she does not have any contraindications described in the exclusion criteria, she should be started on steroids. Methylprednisolone or prednisolone is typically given instead of prednisone, because the liver needs to be able to convert prednisone to its active form, prednisolone.

Is there any evidence for other therapies, such as N-acetylcysteine?

N-acetylcysteine may repress expression of TNF-alpha, act as an anti-oxidant, reducing free-radicals in hepatocytes, and reconstitute glutathione in the liver.

Trials have investigated the utility of N-acytelcysteine (NAC) with generally limited results. The most supportive trial looked at the benefit of adding IV NAC in a double-blinded fashion to oral prednisolone in a group of patients with severe alcoholic hepatitis (DF ≥ 32).[4] While 1-month mortality rates and the rates of hepatorenal syndrome were decreased with NAC versus placebo, the 6-month mortality rates were not statistically different.

Note that other alternative therapies for alcoholic hepatitis are unproven (e.g. propylthiouracil) or associated with higher mortality (inflixamab and etanercept).[3]

What is this patient's prognosis?

In earlier studies of severe alcoholic hepatitis, the 28-day mortality was about 35% without treatment, even though the sickest patients (e.g., those with active GI bleeding or infections) were excluded.[1] Mortality was significantly better in the most recent STOPAH trial -- 18% in those who did not receive steroids.[2] The patient in our case is representative of the patients in the studies reviewed here, and her prognosis without treatment would approximate the numbers above.

Treatment of this acute presentation of alcoholic damage is merely the starting point to long-term impact on prognosis. This patient will require intensive social work and community intervention if she is to alter her eventual prognosis. Seven-year survival rate for patients with alcoholic liver disease who continue to drink is 50%. Abstinence increases this rate to 80%.[3]

III. Questions for Further Discussion

Case (cont.)

After admitting the patient and ruling her out for an acute infection, you decide to start her on prednisolone. She receives counseling on alcohol cessation and is discharged two days later. One week later, she returns to your clinic. She feels fatigued and slightly nauseous, but denies any confusion. She says she is taking her medicine and abstaining from alcohol. On exam, she now has moderate abdominal distention, with shifting dullness, but no asterixis. Her repeat labs are as follows: total bilirubin = 10 mg/dL, AST = 105 U/L, ALT = 49 U/L and creatinine = 1.4 mg/dL.

Is this patient's hepatitis responding to the steroids? Should you continue the prednisolone?

Review the results of the study by Louvet, et al.[5] The authors developed a prognostic model (the "Lille model") incorporating 6 variables, including the trend in bilirubin level, that predicts six-month survival and response to steroids.

The formula is complicated, but an online Lille model calculator is available.[7] According to this model, a score of $\geq$ 0.45 correlates with a 6-month survival of only 25% and a poor response to steroids. One should consider stopping prednisolone in such a patient.

Using the lab values on admission and 1 week later, the patient's Lille model score is 0.15. The patient should complete her course of prednisolone therapy.

If the patient does not respond to therapy, is there a role for orthotopic liver transplantation?

An observational study of 26 patients who underwent transplant for severe alcoholic hepatitis found a higher rate of survival compared to a non-transplanted cohort, with a low rate of relapse in this highly selected group.[6] *Discuss the ethical dilemma of transplanting a patient who has not yet demonstrated abstinence. Transplant centers in the United States generally require 6 months of abstinence before approving transplantation.*

IV. Key Articles

1. Carithers R, *et al.* Methylprednisolone therapy in patients with severe alcoholic hepatitis. *Ann Int Med* 1989; 110: 685-90. ABSTRACT

Background

- Alcoholic hepatitis is a necrotizing inflammatory process
- Results of previous studies on corticosteroids were mixed, with suggestion of benefit seen in patients with more severe hepatitis
- Retrospective analysis of studies found that the Discriminant Function (DF) identified patients at high risk for early mortality:
  --- DF = 4.6 (prothrombin time-control time) + serum bilirubin (mg/dL)
- Methylprednisolone used instead of prednisone, as the latter needs to be converted to the active form (prednisolone) by the liver

Methods

- Randomized, double-blinded, placebo-controlled, multicenter trial
- Inclusion criteria: Clinically diagnosed alcoholic hepatitis *plus*:
  -- Hepatic encephalopathy *or*
  -- DF > 32
- Exclusion criteria:
  -- History of viral hepatitis or prior heroin addiction (note that this study was performed before the discovery of hepatitis C)
  -- Contraindications to steroid therapy, *e.g.*, current gastrointestinal (GI) bleeding requiring transfusion, diabetes requiring insulin, acute infection, acute pancreatitis
  -- Serum creatinine > 2 mg/dL
- Intervention:
  -- Oral or IV methylprednisolone 32 mg/day for 28 days, followed by 16 mg/day for one week and then 8 mg/d for one week, or corresponding placebo
  -- Almost all patients hospitalized for duration of treatment
- Primary endpoint: 28-day mortality

Results:

- N = 66 with one loss to follow-up
- 28-day mortality: 6% in steroid group vs. 35% in placebo group (p = 0.006)
  -- ARR = 29%, NNT = 4

Limitations

- Results should be applied only to patients with severe alcoholic hepatitis

- Extensive exclusion criteria, including viral hepatitis, GI bleeding, acute infection and renal failure
- Patients were presumably not drinking during the course of the study, since they were hospitalized for duration for treatment

2. Thursz M, *et al.* for the STOPAH Trial. Prednisolone or pentoxifylline for alcoholic hepatitis. *N Engl J Med* 2015; 372: 1619-28. FULL TEXT PDF

Methods

- Randomized, double-blinded 2 x 2 factorial design, multi-center trial, intention-to-treat analysis
- Inclusion: DF ≥ 32, recent excess alcohol consumption and a total bilirubin > 4.7 mg/dL.
- Exclusion: jaundice > 3 months, abstinence from alcohol > 2 months, other causes of liver disease; the following conditions resulted in exclusion unless the patient became stable within 7 days: active GI bleed, untreated sepsis, Cr > 5.7 mg/dL, or the requirement of inotropic support.
- Intervention: 4 groups:
  -- Placebo + placebo
  -- Pentoxifylline 400 mg tid + placebo
  -- Prednisolone 40 mg daily + placebo
  -- Pentoxifylline + prednisolone
- All treatments were given for 28 days
- Primary endpoint: 28-day mortality
- Secondary endpoints: mortality or liver transplantation at 90-days and 1-year
- Follow-up: 12 months

Results

- 1,103 patients enrolled
- 28-day mortality
  -- Placebo 17 %
  -- Pentoxifylline 19 %
  -- Prednisolone 14 %
  -- Pentoxifylline-Prednisolone 13 %
- Mortality benefit with prednisolone statistically significant only after adjustment of baseline prognostic factors
- No survival benefit in any group at 90 days and one year
- Infection rates higher in the prednisolone groups (13% vs. 7%)

Limitations

- Trial may have been underpowered to show a difference in the primary outcome (fewer patients enrolled than planned)

- Funding limited following secondary end-points in all patients (192 patients did not have long-term outcome data)

V. Reference Articles

3. Lucey M, Mathurin P, Morgan T. Alcoholic hepatitis. *N Engl J Med* 2009; 360: 2758-69. EXTRACT

Review article on the pathophysiology, diagnosis, treatment and prognosis of alcoholic hepatitis.

4. Nguyen-Khac E, *et al*. Glucocorticoids plus N-acetylcysteine in severe alcoholic hepatits. *N Engl J Med* 2011; 365: 1781-9. FULL TEXT PDF

Methods

- Randomized, non-blinded, controlled, multi-center trial, intention-to-treat analysis
- Inclusion: DF ≥ 32, average alcohol intake of 50 g per day during the preceding 3 months and histologic evidence of alcoholic hepatitis
- Exclusion criteria: viral hepatitis, HIV, hepatorenal syndrome, hepatocellular carcinoma, uncontrolled bacterial infection, or other known cause of liver dysfunction other than alcohol
- Intervention: non-blinded NAC IV for 5 days versus glucose infusion for 5 days
- All patients received prednisolone 40 mg orally for 28 days
- Primary endpoint: 6-month mortality

Results

- 85 patients received prednisolone + NAC; 89 received prednisolone + IV glucose and included in analysis
- 24 patients lost before reaching 6 month follow-up, but were included in ITT analysis
- No statistically significant difference in 6-month mortality: 38% prednisolone vs. 27% NAC + prednisolone
- Secondary endpoints
  -- 1 month mortality: 24 % (prednisolone only) versus 8 % (NAC + prednisolone), p = 0.006; ARR 16 %; NNT 7
  -- 6-month death rate from hepato-renal syndrome: 22 % (prednisolone only) versus 9 % (NAC + prednisolone), p = 0.02; ARR 13 %; NNT 8
- Adverse events:
  -- Infection rate: 42 % (prednisolone only) versus 19 % (prednisolone + NAC)

Limitations

- Non-blinded administration of IV NAC
- High loss to follow-up before time of assessing primary endpoint
- Possibly underpowered to show 6-month mortality benefit

5. Louvet A, *et al.* The Lille model: a new tool for therapeutic strategy in patients with severe alcoholic hepatitis treated with steroids. *Hepatology* 2007; 45: 1348-54. FULL TEXT PDF

Methods

- Cohort study of patients with severe alcoholic hepatitis (DF ≥ 32 or encephalopathy) who were treated with corticosteroids
- Goal of the study was to generate a prognostic model (the "Lille model") using logistic regression analysis, to better predict which patients are more or less likely to respond to steroids
  -- Only objective criteria, such as lab values, were used. Subjective or fluctuating criteria, such as ascites, were excluded from the model.
  -- Primary end-point was 6-month survival.
- 295 patients enrolled in the exploratory cohort and 118 patients enrolled prospectively in the validating cohort.
- Lille model also applied to the results of the last three RCTs comparing steroids to placebo

Results

- Six variables included in the final Lille model: age, albumin, bilirubin on day 0, bilirubin on day 7, renal function and prothrombin time.
- The Lille model was more predictive of 6-month survival than the Child-Pugh and Maddrey scores, with higher AUROC curves in the two cohorts.
- When applied to the last three RCTs of steroids vs. placebo, the Lille model also predicted who would respond to steroids.
- In patients with a score ≥ 0.45:
  -- 6-month survival was only 25% in the cohort study
  -- In the RCTs, steroid- and placebo-treated groups had the same mortality
- In patients with a score < 0. 45:
  -- 6-month survival was 85% in the cohort study
  -- In the RCTs, steroids significantly improved mortality, compared to placebo

6. Mathurin P, *et al*. Early liver transplantation for severe alcoholic hepatitis. *N Engl J Med* 2011; 365: 1790-1800. FULL TEXT PDF

Methods

- Inclusion: DF ≥ 32, no prior history of alcoholic hepatitis, non-responder to medical therapy (Lille score ≥ 0.45), a close supportive family, absence of severe psychiatric conditions and a commitment to lifelong alcohol abstinence
- Intervention: Early liver transplant (defined as prior to demonstration of 6 month of abstinence from alcohol)
- Primary endpoint: 6-month survival compared to a cohort of age, sex, Maddrey's score and Lille score-matched non-transplanted patients

Results

- 26 patients underwent early transplant (without 6-months abstinence from alcohol), constituting less than 2% of patients admitted with severe alcoholic hepatitis
- 6-month survival was higher than 26 randomly selected non-transplanted patients: 77 % versus 23 % $p < 0.001$
- 3 patients resumed drinking (720-1140 days after transplantation)

Limitations

- Non-randomized, small subject size, most patients excluded

VI. Resources

7. LILLE MODEL CALCULATOR. This website also includes calculators for the MELD, Child-Pugh and Maddrey (Discriminant Function) scores.