Glucocorticoids in the treatment of alcoholic hepatitis.

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Outline

- Objectives
- Case
- Background
- Clinical Question
- Literature Evaluation
- Recommendation
- Monitoring

Objectives

- To review the pathophysiology and clinical presentation of alcoholic hepatitis
- To review the treatment options for alcoholic hepatitis
- To evaluate the literature for glucocorticoids in the treatment of alcoholic hepatitis

Case

- ID: JE, 33 yo Caucasian male, wt 64.5 kg, ht 170 cm
- CC: ⇧ weakness & fall → brought to ER via ambulance
- HPI:
  - Jaundice X 10 days
  - ⇧ Abdominal girth X several weeks
  - Anorexia → on-going due to lack of interest in food & financial constraints
- Allergies: none

Case

- SH:
  - Homeless
  - Denies any drug use
  - Smoker: 1/2 –2 packs per day X 15 yrs
  - 26 oz (780 mL) of vodka per day
- FH: estranged from family → unable to attain details
- PMHx: Chronic lower back pain X 5 years, Alcoholism X 14 years
- Rx meds/OTCs/herbals PTA : none

Review of Systems

Transfer from GI service to CTU service	
Vitals	T **37.9°C**, BP 132/66, HR 80, RR 16 (O_2 Sat 100 % on RA)
CNS	Alert & Oriented X 3
EENT	PERRLA, **Scleral icterus**
RESP	Non-remarkable
CVS	S1 & S2 normal
GI	No N/V or abd pain

Review of Systems

Liver	**Hepatomegaly, Ascites** **Total Bili 473, AST 132, ALT 38, ALP 104, GGTP 131, INR 1.6, PTT 62 , Albumin 21** Hep A, B, C neg, Ascitic fluid cultures - no growth
Renal/ GU	Urea 3.7, SCr 75, eGFR 88
MSK/ Skin	**Jaundice**
Heme/ Endo	**WBC 14, Neut 10** , **Hgb 94**, MCV 93 (82-98), **RDW 27 (12.1-14.5)**, **Plt 107** **iron 8,** ferritin 50, B12 535, RBC folate 1134
Fluid/ lytes	Na 135, K 4.5, Cl 100

Current Medications

Indication	Medication
Alcohol withdrawal	CIWA protocol
Insomnia	Zopiclone 3.75 mg qhs prn
Nutritional support	Multivitamin with minerals once daily
Ascites	Spironolactone 200 mg PO daily
	Furosemide 80 mg PO daily

Drug Related Problems

- JE is at increased risk of mortality due alcoholic hepatitis/advanced liver disease and requires a reassessment of therapy.
- JE is at increased risk of complications secondary to alcohol related liver disease and requires a reassessment of therapy.
- JE is at increased risk of VTE, secondary to hospitalization, immobility and smoking, requiring VTE prophylaxis.

Drug Related Problems

- JE has a mixed anemia, secondary to anemia of chronic disease and iron deficiency, requiring treatment.
- JE is at increased risk of COPD, CVD and cancer due to tobacco addiction and requires the need for tobacco cessation therapy and education.

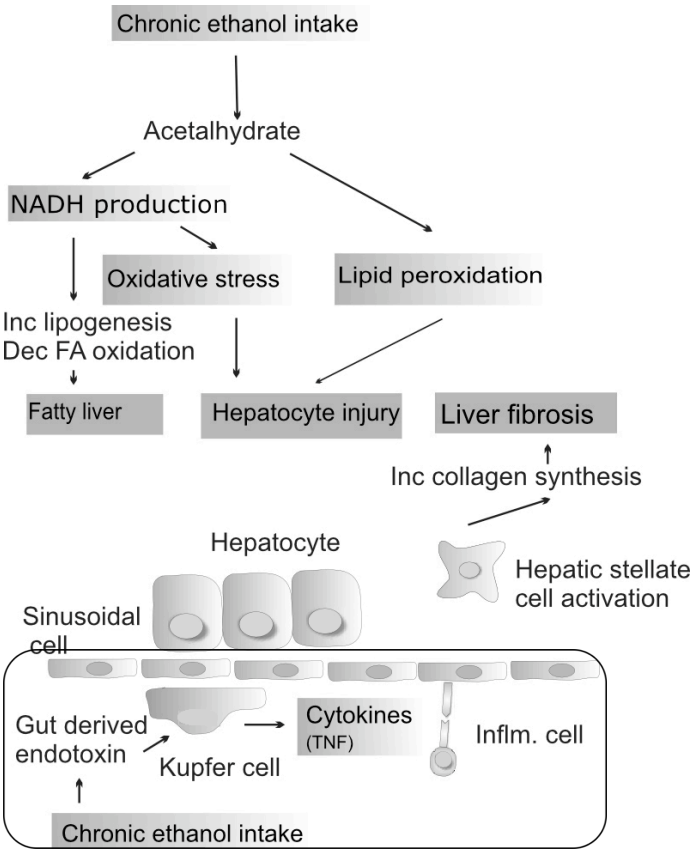
Drug Related Problems

JE is at increased risk of mortality due alcoholic hepatitis/advanced liver disease and requires a reassessment of therapy.

Background

- Alcoholic hepatitis
  - Acute clinical syndrome
  - Jaundice, fever, hepatomegaly, anorexia
  - Often co-exists with portal hypertension, esophageal varices, ascites and hepatic encephalopathy
  - AST: ALT ratio > 2
  - ⇧WBC & neutrophils
  - ⇧bilirubin & INR

Alcoholic Hepatitis



Assessment of alcoholic hepatitis

- Maddrey Discriminant Function (MDF)
  - 4.6 X ($PT_{patient}$-$PT_{control}$) + total bilirubin (μmol/L) /17
- MDF score ≥ 32 = 30 day survival of ~ 50%
- Most commonly used in trials
- Other scoring systems
  - Model for End Stage Liver Disease (MELD)
  - Glasgow
  - Lille
  - Child-Pugh (severity of cirrhosis)

Goals of Therapy

Patient

- Abstinence

Health care team goals

- Normalize temperature, bilirubin, INR, WBC and neutrophils
- Reduce jaundice and improve appetite
- Treat complications (ascites)
- Decrease liver-related mortality
- Minimize adverse drug events
- Improve quality of life

Treatment options for alcoholic hepatitis

- Abstinence (counseling, social support)
- Nutritional support (fluids, calories, vitamins)
- Medications
  - **Glucocorticoids**
  - Pentoxifylline
  - Etanercept
  - Infliximab
  - Propylthiouracil (PTU)

Clinical Question

P	In a 33 year old male with acute alcoholic hepatitis
I	Glucocorticoids
C	No treatment or placebo
O	Decrease signs & symptoms of alcoholic hepatitis & decrease mortality without increasing serious adverse drug events

Literature Search

- Search/ MeSH terms: “alcoholic hepatitis”, “glucocorticoids”
- PubMed: 16 results
- Cochrane Library: 21 results
- Embase: 15 results
- IPA: 25 results
- Manual search: 2 results

Literature Search

- Main result
  - Rambaldi A, Saconato HH, Christensen E, Thorlund K, Wetterslev J, Gluud C. Systematic review: glucocorticosteroids for alcoholic hepatitis-a Cochrane Hepato-Biliary Group systematic review with meta-analyses and trial sequential analyses of randomized clinical trials. Aliment Pharmacol Ther. 2008 ;27(12):1167-78

Rambaldi et al.

- Meta-analysis of 15 trials (n=721)
- Patients: varying severities of alcoholic hepatitis
- Methylprednisolone or prednisolone vs placebo or no treatment
- Primary outcome: mortality
- Secondary outcome: adverse events

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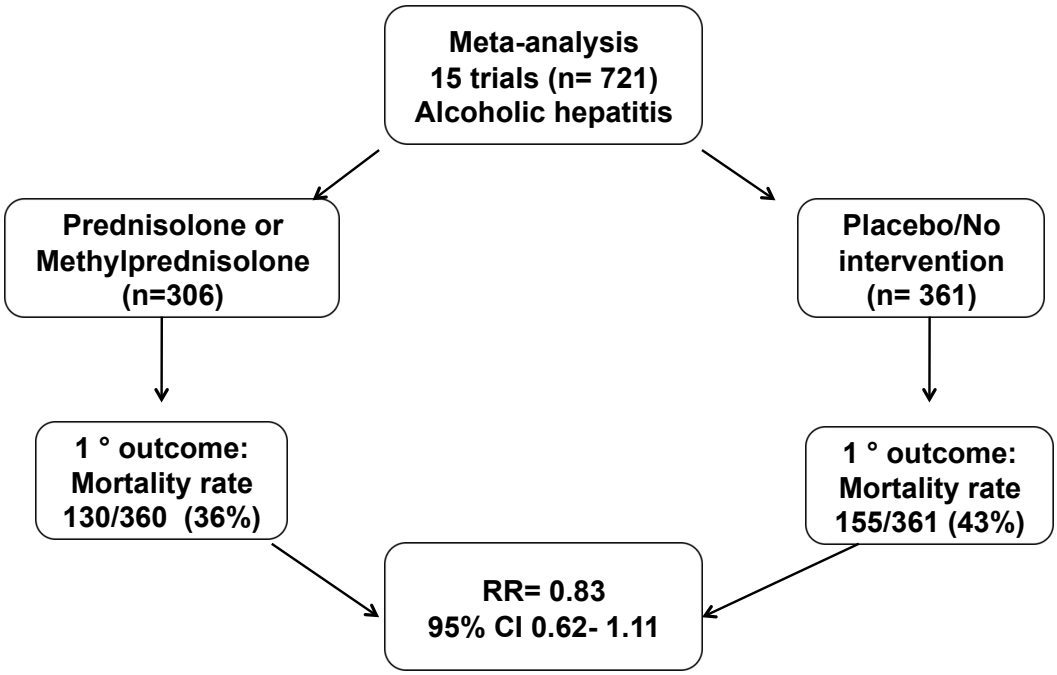

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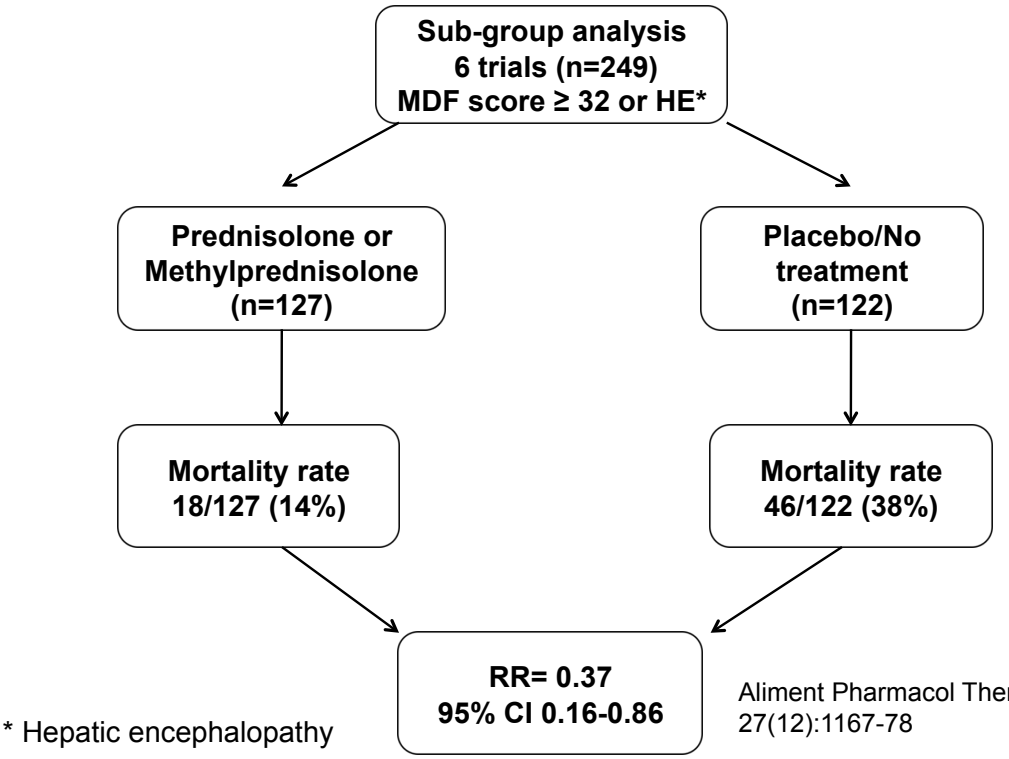

* Hepatic encephalopathy

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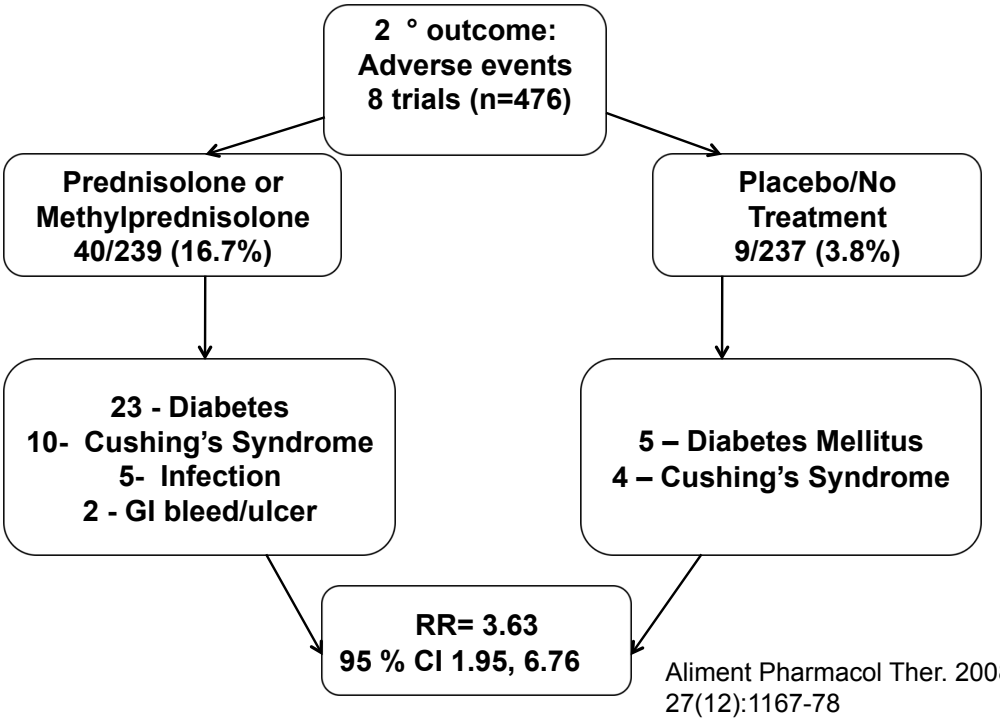

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Limitations

- Outcomes reported
- Only 3 studies were of high methodological quality
- Small sample size despite pooling of 15 trials
- Short duration of trials
- Heterogeneity between trials
- Results of sub-group analysis require confirmation in new trials

Interpretation

- ↓ mortality in sub-group analysis (MDF score ≥ 32 or HE)
  - Relative risk = 0.37 (95% CI 0.16-0.86)
- Short term benefit
  - Most trials → 4 weeks duration
- More adverse events in glucocorticoid group

Clinical Question

P	In a 33 year old male with acute alcoholic hepatitis ✔
I	Glucocorticoids ✔
C	No treatment or placebo ✔
O	Decrease signs & symptoms of alcoholic hepatitis ✕ & decrease mortality ✔ without increasing serious adverse drug events ✔

Treatment Options

Medication	Considerations
Glucocorticoids Prednisolone 40 mg PO daily X 4 weeks then taper	First line option Low cost Can stimulate appetite
Pentoxifylline SR 400 mg PO TID X 4 weeks	Second line option Low Cost Few clinical trials
Etanercept	Effective dose not yet determined High Cost ⇧infections/mortality
Infliximab	
PTU 300 mg PO daily	Not recommended in guidelines Low cost Meta-analysis → no survival benefit

Recommendation

- JE's MDF score ≥ 32
  - 4.6 X (16.7-10.9) + 384 μmol/L /17 = **49**
- Start **prednisolone** 40 mg PO daily X 4 weeks followed by taper.
- Taper over 4 weeks
  - Week 1: 30 mg PO daily
  - Week 2: 20 mg PO daily
  - Week 3: 10 mg PO daily
  - Week 4: 5 mg PO daily

Monitoring

Efficacy	
Clinical improvement - temperature, appetite, jaundice WBC & neutrophils Total bilirubin, ALT, AST INR & PTT Mortality	Daily Every 2-3 days Every 2-3 days Every 2-3 days
Toxicity	
Leukocytosis Hyperglycemia Fluid retention& Ascites Infection Insomnia/Psychosis	Every 2-3 days BGT daily Daily weight Daily Daily

Reassess therapy in one week

Application to practice

In patients with severe alcoholic hepatitis, (MDF score ≥ 32 or hepatic encephalopathy), there is some evidence that glucocorticoids may reduce short term mortality (~ 28 days).

References

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