Considerations in Patients with Alcohol-Induced Liver Cirrhosis

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Chief Complaint: Yellow eyes, chest pain

History of Present Illness: 44 y/o male w/ PMH significant for T2 DM and alcohol-induced liver cirrhosis complicated by ascites presents w/ scleral icterus, chest pain, and bilateral back pain for 2 days. He had been sober since his dx of cirrhosis, but his grandfather passed 1.5 wks ago and he drank a fifth of hard alcohol over 2 days to cope. He was admitted to AMITA Health LaGrange on 12/14 for alcohol withdrawal and depressed mood. He was discharged on 12/18, after which he noted progressive yellowing of his eyes and skin. The chest pain developed 1 day ago and is left-sided, lasts for 45-60 minutes, radiates to his left shoulder and back, and has no apparent trigger. He has also had URI symptoms since discharge, mostly chills and a mild dry cough. He has not used alcohol since his discharge from LaGrange. He has some mild nausea that appears to be chronic in nature. Pt denies abdominal pain, dyspnea, diarrhea, constipation. He does report some increased abdominal girth, but denies urinary symptoms, hematuria, dysuria.

Past Medical History: Alcohol cirrhosis w/ ascites- dx 5/2019; Diabetic polyneuropathy; Type 2 Diabetes Mellitus; Pancreatitis

Past Surgical History: None

Medications: Carvedilol 25 mg PO BID; Furosemide 40mg PO BID; Thiamine 100mg PO Daily; Folic Acid 1mg PO Daily; Spironolactone 50mg PO Daily

Allergies: NKA

Social History: 20-yr hx of EtOH use, a "gallon" of alcohol every few days. Last drink 1.5 wks ago; a fifth of alcohol. Denies tobacco or illicit drug use hx.

Review of Systems: General: Reports chills; Cardio: Reports chest pain; Pulm: Reports cough; GI: Reports nausea, vomiting, jaundice

Vital Signs:

Time	Temp	BP	Pulse	RR
15:03	97.2/36.2	134/66	78	20
13:38	98.1/36.7	105/59	74	20
12:30	97.2/36.2	89/57	72	22

Physical Exam:
General: NAD, A&Ox3
HEENT: **Scleral icterus**, moist mm
Cardio: No JVP noted, normal S1S2, no RCM
Pulm: Normal inspiratory/expiratory, no decreased breath sounds, no WRC
GI: **Firm, distended**, non-tender to palpation, no rebound tenderness, mild ascites on US
GU: No suprapubic or CVA tenderness, suprapubic pain, or flank pain
Neuro: CN 2-12 grossly intact, no focal neurologic deficits
MSK: **Jaundiced skin**, moves all extremities to command, no lower extremity edema

Labs/ Imaging:

Na+	131	AGAP	7	CrCl	63.6	WBC	11.2	HCT	35.0	**AlkPhos**	**431**
Cl-	104	BUN	18	CA	8.7	RBC	3.3	Plat	302	**ALT**	**66**
K+	4.2	Cr	1.64	GLUC	150	MCV	106.0	**TBilli**	**24.9**	**AST**	**164**
CO2	20	eGFR	45.9			HgB	11.9	Billi	18.5	Alb	3.1

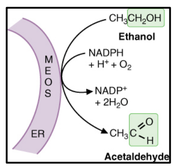
Diagnosis

- In the ED, our patient presented with radiating chest pain to the left shoulder and lower back without any triggers. Cardiac work-up came back negative, so portal hypertension gastritis is the most likely etiology due to PMH of liver cirrhosis. Current plan is to start on proton pump inhibitors and monitor for symptom improvements. As portal hypertension gastritis is the believed etiology, an esophagogastroduodenoscopy (EGD) is considered to assess his gastric mucosa. Carvedilol 25 bid is being given to treat the portal hypertension as well as a variceal bleeding prophylaxis.
- Our patient's most pressing concern is alcohol cirrhosis hepatitis. Labs showed total bilirubin at 24.9, alkaline phosphatase at 431, AST at 164, and ALT at 66. High total bilirubin and alkaline phosphatase suggest liver damage. AST/ALT ratios greater than two suggests liver damaged due to alcohol.[1] Liver function tests along with his history of heavy drinking supports his diagnosis of alcohol cirrhosis. His current treatment plan includes counseling to stop drinking and provide resources with social work. An intensive substance use program is being considered. Since his Maddrey score was 50 (greater than 32), prednisolone was being considered for 28 days with a two-week taper.[2] A liver transplant is currently being considered as well.

Discussion of Disease Process & Clinical Correlations

Alcohol consumption affects the body in a variety of ways and necessitates clinicians account for all current diagnoses, current and future medications, and other nutrition/lifestyle factors.

Figure 1



MEOS Pathway - Inducible 5-10x in chronic alcoholism[3]

- Excess ethanol (alcohol) overwhelms natural metabolism, shunting to the toxic "MEOS" pathway (Figure 1) and generating ROS.[3] Increased metabolism also raises the NADH:NAD ratio in the body, inhibiting the Krebs Cycle and causing excess ketone production. This can cause ketoacidosis,[3] which is especially key as our patient has T2 DM and is thus already at risk.
- A positive feedback cycle of worsening inflammation occurs. Cell damage and death from the above and attempted cellular regeneration causes fibrosis (connective tissue scarring). This narrows vessels and inhibits perfusion, furthering damage. Cirrhosis is the extensive scarring that results.[3]
- Ethanol is a CYP inducer,[3] so all medications should be carefully considered to avoid potential impairment of effect via increased metabolism.
- Patients with alcoholism have high risk of vitamin deficiency due to inadequate diet, malabsorption, and impaired utilization. Chronic alcoholism is the main cause of Wernicke Encephalopathy due to thiamine (Vitamin B1) deficiency. Physical exam indications include oculomotor dysfunction and gait ataxia. Patients should be given IV or PAR thiamine immediately.[4]
- Alcoholism has long history of being considered as "self-inflicted," and patients with Alcoholic Liver Disease (ALD) are often seen as poor candidates for liver transplantation (LT) for fear of relapse. One study estimated there are 100,000 potential candidates for LT in the USA. In 2018, 10,000 had been referred and 3,673 were on the waiting list. Only 1,200 received an LT that year. Despite this, survival rates are comparable between ALD patients and those with other causes of end-stage liver disease (Table 1).[5]

Table 1 - LT survival (European Liver Transplant Registry)[5]

n	Etiology	1 yr	5 yr	10 yr
		%		
15019	AC	86	73	59
1790	AC + HCV	85	69	54
6507	Acute liver failure	70	64	58
10753	HCV	80	65	53
4187	HBV	83	74	68
9122	Cirrhosis + HCC	83	62	49
9114	Cholestasis	87	78	70
1892	AIH	85	76	67
468	Hemochromatosis	76	66	53

Note - AC: Alcoholic cirrhosis

Current Research & New Treatments

- Little has changed in the treatment options for ALD patients in the last 40 years. Abstinence from consuming alcohol is the foundation of treatment, primarily to prevent disease progression. This can resolve alcoholic fatty liver disease and positively affect the survival rate for patients with cirrhotic livers. Corticosteroids have also proved to extend the lives of ALD patients. However, approximately 40% of ALD patients do not respond to corticosteroids and others have contraindications. For these patients, the only other option is Pentoxifylline (PTX), a drug that has anti-inflammatory properties and has been shown to reduce the incidence of Hepatorenal Syndrome and thereby decrease mortality. ALD patients are also prone to nutritional deficiencies, which should be supported through supplementation.[6]
- Current research in new treatments for ALD is focused on macrophages as possible targets due to their association with inflammation and fibrosis. Several drugs are currently in clinical trials. Research on the ASK-1 inhibitor Selonsertib and its ability to inhibit macrophage activation has been focused on patients with Non-Alcoholic Fatty Liver Disease, but a new study comparing the supplementation of prednisolone with Selonsertib is underway in ALD patients. Caspase inhibitors have been shown to also inhibit macrophage activation and decrease hepatocyte apoptosis. A recent phase-2 clinical trial on the caspase inhibitor, Emricasan, showed that cirrhotic patients had better liver function compared to patients taking a placebo. These are just a few of the drugs currently being examined for their ability to improve liver function in ALD patients. New findings and recommendations in the treatment of ALD patients could be made as soon as this year.[7]

Conclusion

- For patients with ALD, the most immediate action is to provide support so they can stop consuming alcohol. Abstinence from alcohol can improve prognosis and disease progression and allow patients to qualify for LT in the future.
- Other considerations include monitoring for vitamin deficiency, life-threatening conditions such as ketoacidosis, and medications (to avoid further liver damage or toxicity from CYP induction). Finally, we can address stigma toward alcoholic liver disease and support patients to achieve lifestyle modifications.

References

1. Marion, DW. Approach to the patient with abnormal liver biochemical and functional tests. In: UpToDate, Post, TW (Ed), *UpToDate*, Waltham, MA, 2020.
2. Marion, DW. Management and Prognosis of Alcohol Hepatitis. In: UpToDate, Post, TW (Ed), *UpToDate*, Waltham, MA, 2020.
3. Lieberman, M. "Metabolism of Ethanol." Marks' Basic Biochemistry: A clinical approach. 5th ed, 2018.
4. So, Yuen. "Wernicke encephalopathy." In: UpToDate, Post, TW (Ed), *UpToDate*, as of 2016 Aug 30.
5. Marroni, C., et Al. "Liver transplantation and alcoholic liver disease: History, controversies, and considerations." *World Journal of Gastroenterology* 2018 Jul 14; 24(26): 2785-2805.
6. Singh, Sukhpreet et al. "Treatment options for alcoholic and non-alcoholic fatty liver disease: A review." *World Journal of Gastroenterology* vol. 23,36 (2017): 6549-6570.
7. Vonghia, Luisa et al. "Targeting Myeloid-Derived Cells: New Frontiers in the Treatment of Non-alcoholic and Alcoholic Liver Disease." *Frontiers in immunology* vol. 10 563. 27 Mar. 2019

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