گزارش صبحگاهی

اپروچ به آقای ۳۲ ساله با اختلال آنزیم کبدی در درمانگاه پزشکی خانواده

ارائه دهنده: سوگل علی‌کرمی

استاد راهنما: خانم دکتر زینب فنی

Patient ID

آقای ۳۲ ساله

اهل و ساکن تهران

شغل: دانشجو

مجرد

منبع شرح حال بیمار بوده و قابل اعتماد است.

Chief Complaint

آقای ۳۲ ساله با شکایت بالارفتن آنزیم‌های کبدی از ۱/۵ ماه قبل

Present illness

- بیمار آقای ۳۲ساله که با شکایت اصلی بالا رفتن آنزیم های کبدی از ۱/۵ ماه قبل که به درمانگاه پزشکی خانواده مراجعه کرده است. بیمار سابقه ای از تهوع، استفراغ، بی حالی، خارش، کبودی و خونریزی و زردی ذکر نمی‌کند. سابقه مسافرت اخیر، مصرف آب آلوده و رابطه جنسی پرخطر اخیر نداشته است.
- سابقه درد در ناحیه RUQ از دو ماه قبل می‌دهند. درد گهگاهی خفیف که به جایی انتشار ندارد. به غذا خوردن ارتباط ندارد و پوزیشنال نیست. درد اکنون تخفیف پیدا کرده است.

Past Medical History

- سابقه هایپر تری گلیسیریدمی
- هایپرتایروئیدیسم
- در سال ۱۳۹۶، ۱۳۹۸ و ۱۴۰۱ به گفته بیمار با تشخیص سوزاک سه مرتبه تحت درمان آنتی بیوتیکی قرار گرفته‌اند. بیمار دکر می‌کنند بررسی از نظر HIV, HBV, HCV منفی بوده است.
- DM(-)
- HTN(-)
- IHD(-)

Past Surgical History: Negitive

Drug History

لووتیروکسین ۵۰ میکروگرم روزانه یک عدد ۵ روز در هفته

سرترالین ۲۰ میلیگرم یک دوم قرص روزانه

تری فلوئوپرازین ۱ میلیگرم روزانه یک عدد

لیورگل تا ۱۰ روز قبل

بیماراز ۵ ماه قبل به علت آکنه صورت زیر نظر متخصص پوست تحت درمان با راکوتان یک عدد به صورت یک روز در میان قرار گرفتند. باافزایش TGو ALTاز حدود سه هفته قبل راکوتان راقطع کرده اند .

بیمار سابقه مصرف داروی گیاهی و مکمل‌های ورزشی را ذکر نمی‌کند.

- Allergy History: Food(-) Drug(-) Pet(-)
- Family History: HLP in his mother
- Social History and Personal History: Smoking(-) Alcohol (-) Opium (-)

مسافرت اخیر و تماس با آب آلوده (-)

ارتباط جنسی مشکوک اخیر(-)

Review of Systems(R.O.S)

عمومی: تب(-) خستگی(-) ضعف(-) بی‌اشتهایی(-) لرز(-)

پوست: زخم(-) توده(-) راش(-) خارش(-) خشکی(+) تغییرات ناخن(-) تغییرات و ریزش مو(-) اسکار(-) اریتم(-) سوزش(-) پتشی(-)، پورپورا(-)، اکیموز(-)

HEENT:

Head: سر درد(-) سرگیجه(-) ضربه به سر(-) احساس سبکی سر(-) احساس سنگینی سر(-) سیاهی رفتن چشم‌ها(-)

Eyes: استفاده از عینک(-) درد(-) قرمزی(-) اشک ریزش(-) ترشح(-) دوبینی(-) تاری دید(-) خارش(-) خشکی(-)

Ears: درد (-) عفونت (-) ترشح(-) وز وز گوش(-) کم شنوایی(-)

Nose and Sinuses: گرفتگی و خونریزی(-) آبریزش(-) خشکی بینی(-) سرماخوردگی ومکرر(-) تروما و شکستگی(-)

Review of Systems(R.O.S)

Throat (mouth and pharynx): گلودرد (-) خشکی دهان(-) آفت(-) گرفتگی صدا(-) زخم زبان و دهان(-) خونریزی لثه(-) تبخال(-)

گردن: توده(-) درد(-) سفتی(-) اسکار(-) عدم قرینگی(-) گواتر(-)

غدد لنفاوی: تورم و برجستگی نواحی گردن، آگزیلاری و اینگوینال(-)

دستگاه تنفس: سرفه(-) خلط(-) تنگی نفس(-) خس خس(-) هموپتزی(-)

قلبی و عروقی: درد قفسه سینه(-) تپش قلب(-) ارتوپنه(-) PND(-)

Review of Systems(R.O.S)

- اندام‌ها: ادم(-) پارستزی (-) ضعف دراندام‌ها(-)
- عروق محیطی: لنگش(-) رینود(-)
- دستگاه گوارش: تهوع(-) سوزش سر دل(-) استفراغ(-) اسهال(-) یبوست(-) رکتوراژی(-) سیری زودرس(-) دیسفاژی(-) ادینوفاژی(-) رگورژیتاسیون(-) درد شکمی(-) تغییر رنگ و کالیبر مدفوع(-) ملنا و هماتوشزی(-) نفخ(-) تغییر در عادت دفع(-)
- دستگاه ادراری: پلی اوری(-) تکرر ادرار(-)دیزوری(-) تغییر رنگ ادرار(-) درد پهلو(-) urgency(-) هماچوری(-)

Physical Exam

General Appearance :

Height: 180cm Weight : 80 kg BMI =24.7 GCS: 15

بیمار آقای جوان، هوشیار و Oriented بوده و به سوالات پاسخ می‌دهد.

Vital signs: PR: 77 RR: 18 BP: 110/60

Physical Exam

ضایعه پوستی، اکیموز، پورپورا و پتشی دیده نشد.

ملتحمه pale نیست. اسکلرا ایکتریک نیست.

تنفس قرینه است. و دیسترس تنفسی ندارد. سمع ریه‌ها نرمال است و صدای اضافه یا کاهش صدای یکطرفه ندارد.

در سمع S1 و S2 شنیده می‌شود و سوفلی مسموع نیست.

نبض اندام‌ها پر و قرینه است.

شکم قرینه است. کاپوت مدوزا وجود ندارد. در لمس شکم نرم است و تندرنس، ریباند تندرنس و گاردینگ وجود ندارد و توده‌ای احساس نمی‌شود. دق شکم تیمپان است. هپاتومگالی و اسپلنومگالی وجود ندارد.

Lab data

	1402/4/18	1402/6/28	1402/7/22
WBC	7100	7300	
RBC	5*10^6	4.9*10^6	
HGB	14.9	13.9	
HCT	44.1	42.5	
Neut	67.4%	56.8%	
Lymph	26.9%	35.5%	
PLT	271000	265000	
ALT	44	147	233
AST	27	60	97
ALP	141	144	145
FBS		115	
Urea		38	
Cr	1.1	1.1	
TG	168	595	404
Cholestrol		236	252
HDL	33	37	
LDL	101	110	

Problem List

آقای ۳۲ ساله با درد خفیف گهگاهی در RUQو با افزایش آنزیم‌های کبدی با ارجحیت ALTو TGو cholsetrolافزایش

یاقته به دنبال مصرف داروی راکوتان

در سونوگرافی بعمل امده از شکم :

کبد با اندازه و شکل طبیعی رویت شد و ضایعات Cystic و یا Solid در آن رویت نشد.

اکوژنیسیته پارانشیم کبد به صورت منتشر افزایش یافته می باشد. (کبد چرب گرید II).

تطابق با LFT توصیه می شود.

مجاری صفراوی داخل و خارج کبدی و ورید پورت دیامتر نرمال دارند.

کیسه صفرا با ضخامت جداری نرمال رویت شد. سنگ و اسلاج در داخل آن رویت نشد.

اندازه، اکوژنیسیته پارانشیمال و شکل طحال طبیعی می باشد.

در سونوگرافی از پانکراس، آئورت و پاراآئورت در حد قابل بررسی ضایعه مشخصی رویت نگردید.

ابعاد، حدود و پاترن هر دو کلیه طبیعی است. اکوژنیسته پارانشیم هر دو کلیه نرمال رویت می شود.

کلیه چپ با سایز ۱۰۳ mm و با ضخامت پارانشیم ۱۳ mm رویت شد.

کلیه راست با سایز ۱۱۹ mm و با ضخامت پارانشیم ۱۱ mm رویت شد.

سنگ و هیدرونفروز و ضایعه فضاگیر Solid و Cystic در کلیه ها مشاهده نشد.

مایع آزاد در حفره شکم مشهود نیست .

Liver enzymes

- Serum aminotransferases: alanine aminotransferase (ALT, formerly called SGPT) and aspartate aminotransferase (AST, formerly called SGOT)
- Alkaline phosphatase
- Gamma-glutamyl transpeptidase (GGT)
- 5'-nucleotidase
- Lactate dehydrogenase (LDH)

Aminotransferases

- In adults, normal ALT levels range from 29 to 33 units/L for males and 19 to 25 units/L for females. Levels above these values should be assessed for underlying liver disease
- The sensitivity and specificity of the serum aminotransferases (formerly transaminases), particularly serum ALT, for differentiating those with liver disease from those without liver disease depend on the cutoff values chosen to define an abnormal test.

- AST is present in the liver and other organs including cardiac muscle, skeletal muscle, kidney, and brain. In children, levels decline with age, more so in girls than boys after age. ALT is present primarily in the liver, and thus is a more specific marker of hepatocellular cell injury. ALT levels correlate with the degree of abdominal adiposity, and at least two large studies have suggested that the cutoff values should be adjusted for sex and body mass index (but not age). However, most patients identified using the lower cutoff values have only mild liver disease or no identifiable cause of the abnormal laboratory values. Thus, the overall benefit of the proposed modifications is unclear since it would translate into a large increase in the absolute number of patients who would require evaluation for an uncertain clinical benefit

- Alkaline phosphatase — Serum alkaline phosphatase is derived predominantly from the liver and bones. An elevated alkaline phosphatase can be fractionated to determine if it originates from the liver or bones, although in practice a liver source is usually confirmed by the simultaneous elevation of other measures of cholestasis (eg, gamma-glutamyl transpeptidase).
- Women in the third trimester of pregnancy, for example, have elevated serum alkaline phosphatase levels due to an influx into blood of placental alkaline phosphatase. Individuals with blood types O and B can have elevated serum alkaline phosphatase levels after eating a fatty meal due to an influx of intestinal alkaline phosphatase. Infants and toddlers occasionally display transient marked elevations of alkaline phosphatase in the absence of detectable bone or liver disease. Alkaline phosphatase elevations have been noted in patients with diabetes mellitus.There are also reports of a benign familial occurrence of elevated serum alkaline phosphatase due to intestinal alkaline phosphatase.
- Alkaline phosphatase levels also vary with age. Alkaline phosphatase levels are generally higher in children and adolescents because of physiologic osteoblastic activity. Levels may be up to three times higher than in healthy adults, with maximum levels in infancy and adolescence, coinciding with periods of maximum bone growth velocity .Also, the normal serum alkaline phosphatase level gradually increases from age 40 to 65 years, particularly in women.

Patterns of liver test abnormalities

- Hepatocellular pattern:

Disproportionate elevation in the serum aminotransferases compared with the alkaline phosphatase

Serum bilirubin may be elevated

Tests of synthetic function may be abnormal

- Cholestatic pattern:

Disproportionate elevation in the alkaline phosphatase compared with the serum aminotransferases

Serum bilirubin may be elevated

Tests of synthetic function may be abnormal

- Isolated hyperbilirubinemia: As the term implies, patients with isolated hyperbilirubinemia have an elevated bilirubin level with normal serum aminotransferases and alkaline phosphatase

The R value (also known as the R factor) can be used to help determine the likely type of liver injury (hepatocellular versus cholestatic) in patients with elevated aminotransferases and alkaline phosphatase.

R value = (ALT ÷ ULN ALT) / (alkaline phosphatase ÷ ULN alkaline phosphatase)

The R value is interpreted as follows:

- ≥5: Hepatocellular injury
- >2 to <5: Mixed pattern
- ≤2: Cholestatic injury

AST to ALT ratio

- Most causes of hepatocellular injury are associated with a serum AST level that is lower than the ALT. An AST to ALT ratio of 2:1 or greater is suggestive of alcoholic liver disease, particularly in the setting of an elevated gamma-glutamyl transpeptidase
- However, the AST to ALT ratio is occasionally elevated in an alcoholic liver disease pattern in patients with nonalcoholic steatohepatitis, and it is frequently elevated (although not greater than two) in patients with hepatitis C who have developed cirrhosis. In addition, patients with Wilson disease or cirrhosis due to viral hepatitis may have an AST that is greater than the ALT, although in patients with cirrhosis the ratio typically is not greater than two.

- Acute liver failure — Acute liver failure is characterized by acute hepatocellular injury with liver tests typically more than 10 times the upper limit of normal, hepatic encephalopathy, and a prolonged prothrombin time (international normalized ratio greater than or equal to 1.5).
- Marked elevation without liver failure — Patients with marked or severe elevations in their aminotransferase levels (approximately 15 times the upper limit of normal or higher) often have acute hepatitis, although in some cases, there may be underlying chronic liver disease (eg, Wilson disease or an acute exacerbation of hepatitis B virus). Massive elevations in aminotransferases (>5,000 U/L) are usually due to ischemic or drug-induced hepatitis. Other causes of massive elevations in AST include rhabdomyolysis and heat stroke.

- Mild to moderate elevation

Mild to moderate elevations of the serum aminotransferases (less than 15 times the upper limit of normal) are often seen with chronic liver disease, although transient elevations may also be seen in patients with mild hepatic insults (eg, intake of nontoxic doses of acetaminophen).

Differential diagnosis of mildly and moderately elevated serum aminotransferases (<15 times upper limit of normal)

Hepatic disease		Nonhepatic disease
ALT predominant (AST/ALT <1)	**AST predominant (AST/ALT ≥1)**	
Drug-induced liver injury	Alcoholic hepatitis	Muscle injury (strenuous exercise, myopathy)
Chronic viral hepatitis (HBV, HCV)	Cirrhosis due to viral hepatitis or NAFLD	Adrenal insufficiency
Occupational, toxin-related hepatocellular damage	Wilson disease	Myocardial infarction, heart failure
Autoimmune hepatitis		Anorexia nervosa
NAFLD		Thyroid disease
Genetic disorders ▪ Wilson disease ▪ Hemochromatosis ▪ Alpha-1 antitrypsin deficiency		Celiac disease
Congestive hepatopathy		Macro AST
Malignant infiltration of the liver		

Evaluation of isolated mild chronic elevation of serum aminotransferases*

Step 1: Initial evaluation
Review possible links to medications, herbal therapies, or recreational drugs
Screen for alcohol abuse (history, screening instruments, AST/ALT ratio >2:1)
Obtain serology for hepatitis B and C (HBsAg, anti-HBs, anti-HBc, anti-HCV)
Screen for hemochromatosis (Fe/TIBC >45 percent)
Evaluate for fatty liver (AST/ALT usually <1, obtain RUQ ultrasonography)
Step 2: Second-line evaluation (if initial evaluation is unrevealing)
Consider autoimmune hepatitis, particularly in women and in those with a history of other autoimmune disorders (check serum protein electrophoresis; obtain ANA and ASMA if positive)
Obtain thyroid function tests (TSH if hypothyroidism is suspected; otherwise, obtain serum TSH, free T4, and T3 concentrations)
Consider celiac disease (especially in patients with a history of diarrhea or unexplained iron deficiency: serum IgA anti-tissue transglutaminase antibodies)
Step 3: Evaluation for uncommon causes (if second-line evaluation is unrevealing)
Consider Wilson disease, especially in those <40 years of age (check serum ceruloplasmin, evaluate for Kayser-Fleischer rings)
Consider alpha-1 antitrypsin deficiency, especially in patients with a history of emphysema out of proportion to their age or smoking history (obtain alpha-1 antitrypsin level)
Consider adrenal insufficiency (8 am serum cortisol and plasma ACTH, high-dose ACTH stimulation test)
Exclude muscle disorders (obtain creatine kinase or aldolase)
Step 4: Obtain a liver biopsy or observe (if no source identified after steps 1 to 3)
Observe if ALT and AST are less than twofold elevated
Otherwise, consider a liver biopsy

Drug-induced liver injury

- Over 1000 medications and herbal products have been implicated in the development of drug-induced liver injury (DILI), and the list continues to grow. The National Institutes of Health maintains a searchable database of drugs, herbal medications, and dietary supplements that have been associated with DILI. Herbal products associated with DILI are discussed separately.
- The most common drug implicated in acute DILI in the United States is acetaminophen, followed by antibiotics. Worldwide, amoxicillin-clavulanate is one of the most commonly reported causes of DILI

Classifications of drug-induced liver injury

Type of classification	Examples
Clinical laboratory	Hepatocellular
	Cholestatic
	Mixed hepatocellular/cholestatic
Mechanism of hepatotoxicity	Direct hepatotoxicity
	Idiosyncratic
	Immune-mediated
	Metabolic
Histologic findings	Cellular necrosis or apoptosis
	Cholestasis
	Steatosis
	Fibrosis
	Phospholipidosis
	Granulomatous
	Sinusoidal obstruction syndrome

Acute injury

Hepatocellular
Acarbose
Acetaminophen
Allopurinol
Aspirin
Bupropion
Bromfenac
Carbon tetrachloride
Diclofenac
Ethanol
Fluoxetine
Halothane
Iron sulfate
Isoniazid
Ketoconazole
Lisinopril
Losartan
Methyldopa
Nefazodone
Nevirapine
Nonsteroidal anti-inflammatory drugs
Paroxetine
Phenytoin
Pyrazinamide
Rifampin
Risperidone
Ritonavir
Sertraline
Statins
Tetracycline
Trazodone
Thiazolidinediones
Trovafloxacin
Valacyclovir
Valproate
Varenicline

Acute Injury

Cholestasis
Amiodarone
Amoxicillin-clavulanate
Angiotensin-converting enzyme inhibitors
Anabolic steroids
Azathioprine
Azithromycin
Captopril
Carbamazepine
Chlorpromazine
Clopidogrel
Cytarabine
Diclofenac
Dicloxacillin
Efavirenz
Erythromycin
Estrogens
Ethanol
Ezetimibe
Flutamide
Irbesartan
Ketoconazole
Nafcillin
Naproxen
Nevirapine
Phenothiazines
Rifampin
Rosiglitazone
Sulfonylureas
Sulindac
Terbinafine
Trimethoprim-sulfamethoxazole
Tricyclics
Troglitazone

Acute Injury

Mixed
Amitriptyline
Azathioprine
Captopril
Carbamazepine
Clindamycin
Cyproheptadine
Enalapril
Flutamide
Ibuprofen
Nitrofurantoin
Phenobarbital
Phenothiazines
Phenytoin
Sulfonamides
Trazodone
Sulfonamides
Verapamil

Chronic injury

Cholestasis
5-fluorodexoyuridine
Amitriptyline
Ampicillin
Amoxicillin-clavulanate
Anabolic steroids
Azithromycin
Carbamazepine
Chlorpromazine
Chlorpropamide
Clindamycin
Cyproheptadine
Erythromycin
Floxuridine
Flucloxacillin
Haloperidol
Imipramine
Oral contraceptives
Organic arsenicals
Prochlorperazine
Phenytoin
Sulpiride
Tenoxicam
Trimethoprim-sulfamethoxazole
Thiabendazole
Tolbutamide
Tetracycline
Tricyclic antidepressants
Zonisamide

Chronic injury

Microvesicular steatosis
Amiodarone
Camphor
Cocaine
Didanosine
Ethanol
Methotrexate
NRTIs
Piroxicam
Stavudine
Tetracycline
Tolmetin
Valproic acid
Zidovudine

Steatohepatitis
Amiodarone
Diethylaminoethoxyhexestrol
Ethanol
Irinotecan
L-asparaginase
Perhexiline maleate
Tamoxifen
Valproic acid

Chronic injury

Granulomas
Allopurinol
Amiodarone
Carbamazepine
Cephalexin
Dapsone
Diazepam
Diclofenac
Diltiazem
Gold
Hydralazine
Interferon
Isoniazid
Mesalamine
Methyldopa
Nitrofurantoin
Penicillamine
Penicillin
Phenytoin
Procainamide
Quinidine
Rosiglitazone
Sulfonamides
Sulfonylureas

Hepatic venous outflow obstruction (Budd-Chiari syndrome)
Oral contraceptives
Sinusoidal obstruction syndrome
Azathioprine
Busulfan
Chemotherapeutic agents (eg, oxaliplatin)
Cyclophosphamide
Imuran
Mercaptopurine
Oral contraceptives
Pyrrolizidine alkaloids (found in herbal remedies)
Tetracycline
Vitamin A
Fibrosis
Ethanol
Methotrexate
Methyldopa

Phospholipidosis
Amiodarone
Chloroquine
Chlorpheniramine
Chlorpromazine
Perhexiline maleate
Thioridazine

Peliosis hepatis
Anabolic steroids
Arsenic
Azathioprine
Danazol
Diethylstilbestrol
Hydroxyurea
Mercaptopurine
Oral contraceptives
Tamoxifen
Vinyl chloride
Vitamin A

Autoimmune hepatitis
Clometacin
Diclofenac
Fenofibrate
Methyldopa
Minocycline
Nitrofurantoin
Papaverine
Phenytoin
Propylthiouracil
Statins

Chronic hepatitis
Diclofenac
Lisinopril
Methyldopa
Minocycline
Nitrofurantoin
Sulfonamides
Tamoxifen
Trazodone
Uracil

Neoplasm
Anabolic steroids
Arsenic
Carbamazepine
Danazol
Inorganic copper
Oral contraceptives
Polyvinyl chloride
Potassium arsenite
Radium
Thorotrast
Vinyl chloride

Ischemic necrosis
Ergot

Clinical presentation

DILI is often characterized by the type of hepatic injury: hepatocellular (cytotoxic) injury, cholestatic injury, or a mixed picture (which includes features of both hepatocellular injury and cholestatic injury). The type of injury is reflected by the pattern of liver test abnormalities.

●Hepatocellular injury (hepatitis):
Disproportionate elevation in the serum aminotransferases compared with the alkaline phosphatase
Serum bilirubin may be elevated
Tests of synthetic function may be abnormal

●Cholestatic injury (cholestasis):
Disproportionate elevation in the alkaline phosphatase compared with the serum aminotransferases
Serum bilirubin may be elevated
Tests of synthetic function may be abnormal

DILI is considered acute if the liver tests have been abnormal for less than three months and chronic if they have been abnormal for more than three months

CLINICAL MANIFESTATIONS

- Acute presentations of drug-induced liver injury (DILI) include mild asymptomatic liver test abnormalities, cholestasis with pruritus, an acute illness with jaundice that resembles viral hepatitis, and acute liver failure. Chronic liver injury can resemble other causes of chronic liver disease, such as autoimmune hepatitis, primary biliary cirrhosis, sclerosing cholangitis, or alcoholic liver disease. In some patients, chronic injury secondary to DILI progresses to cirrhosis.

- DILI cholestasis is defined as an elevated alkaline phosphatase (ALP) >2 times the upper limit of normal and/or an alanine aminotransferase (ALT) to ALP ratio of less than 2. Injury is considered to be mixed if the ALT/ALP ratio is greater than 2 but less than 5 and hepatocellular if this ratio is >5. The presence of jaundice (serum bilirubin >2 times the upper limit of normal) in association with an elevation in serum aminotransferases (>3 times the upper limit of normal) is associated with a worse prognosis. In this setting, the mortality is as high as 14 percent

Classification of liver test abnormalities

Hepatitis (hepatocellular)	ALT ≥3 x ULN	R ≥5
Cholestasis	ALP ≥2 x ULN	R ≤2
Mixed	ALT ≥3 x ULN ALP ≥2 x ULN	R >2 to <5

Symptoms and examination findings

- Many patients with DILI are asymptomatic and are only detected because of laboratory testing. Patients with acute DILI who are symptomatic may report malaise, low-grade fever, anorexia, nausea, vomiting, right upper quadrant pain, jaundice, acholic stools, or dark urine. In addition, patients with cholestasis may have pruritus, which can be severe, leading to excoriations from scratching. Hepatomegaly may be present on physical examination. In severe cases, coagulopathy and hepatic encephalopathy may develop, indicating acute liver failure. Patients with chronic DILI may go on to develop significant fibrosis or cirrhosis and have signs and symptoms associated with cirrhosis or hepatic decompensation (eg, jaundice, palmar erythema, and ascites).
- Patients with DILI may also have signs and symptoms of a hypersensitivity reaction, such as a fever and rash, or a mononucleosis-like illness (pseudomononucleosis). In some cases, patients will have evidence of toxicity to other organs (eg, bone marrow, kidney, lung, skin, and blood vessels).

DIAGNOSIS

- Nonspecific symptoms developing after introduction of a drug (such as nausea, anorexia, malaise, fatigue, right upper quadrant pain, or pruritus) may indicate drug toxicity and should prompt an evaluation for drug-induced liver injury (DILI). The diagnosis includes obtaining a thorough history and performing blood tests to look for other causes of hepatic injury. If there is evidence of cholestasis, imaging to rule out biliary obstruction is also indicated. If testing for alternative causes of liver injury is negative and the patient has been exposed to a drug known to be associated with hepatic injury, we typically do not proceed with a liver biopsy. However, if the diagnosis remains uncertain (particularly in the setting of acute liver failure) or if there is clinical evidence of chronic liver disease, a liver biopsy should be obtained. A transjugular approach may be needed in patients with a coagulopathy.

The key elements for attributing liver injury to a drug include:

- Drug exposure preceded the onset of liver injury (although the latent period is highly variable)
- Underlying liver disease is excluded
- Stopping the drug leads to improvement in the liver injury
- Rapid and severe recurrence may occur if there is repeated exposure to the drug (however, rechallenge is not advised)

Another factor that supports a diagnosis of DILI is hepatic injury occurring in the setting of exposure to a drug with a history of causing DILI in other patients

MANAGEMENT

- The primary treatment for drug-induced liver injury (DILI) is withdrawal of the offending drug. Early recognition of drug toxicity is important to permit assessment of severity and monitoring for acute liver failure. Few specific therapies have been shown to be beneficial in clinical trials. Two exceptions are the use of N-acetylcysteine for acetaminophen toxicity and L-carnitine for cases of valproic acid overdose.
- Glucocorticoids are of unproven benefit for most forms of drug hepatotoxicity, although they may have a role for treating patients with hypersensitivity reactions. Our practice is to give glucocorticoids to patients with hypersensitivity reactions who have progressive cholestasis despite drug withdrawal or who have biopsy features that resemble those seen in autoimmune hepatitis. In addition, we give glucocorticoids to patients with extrahepatic manifestations of a hypersensitivity reaction that warrant glucocorticoid treatment (eg, severe pulmonary involvement in patients with DRESS [drug reaction with eosinophilia and systemic symptoms]).
- In patients with cholestatic liver disease and pruritus, treatment with a bile acid sequestrant may relieve the pruritus.

- Patients should be followed by serial biochemical measurements until the liver tests return to normal. Hepatology consultation should be considered if there is concern that the patient may be developing acute liver failure (eg, if the patient shows signs of hepatic encephalopathy or coagulopathy), if there are signs of chronic liver disease, or if the diagnosis remains uncertain after an initial evaluation. In addition, patients with evidence of acute liver failure should be transferred to a transplant center early in the course of the illness. The development of jaundice (bilirubin greater than two times the upper limit of normal) in the setting of an alanine aminotransferase greater than three times the upper limit of normal following introduction of a drug potentially portends a poor prognosis and should also prompt immediate referral to a center with expertise in hepatology.

PROGNOSIS

Acute liver injury

The majority of patients with drug-induced liver injury (DILI) will experience complete recovery once the offending medication is stopped. In the setting of cholestatic injury, jaundice can take weeks to months to resolve.

Factors associated with a poorer prognosis in patients with hepatocellular injury include:

- The development of jaundice (bilirubin greater than two times the upper limit of normal) in the setting of an alanine aminotransferase greater than three times the upper limit of normal. The mortality rate in this setting can be as high as 14 percent (80 percent if acute liver failure develops and the patient does not undergo liver transplantation). However, patients who recover from acute DILI with jaundice generally have a favorable prognosis, although some go on to develop progressive chronic liver disease.
- Acute liver failure due to antiepileptics in children.
- Acute liver failure due to acetaminophen requiring hemodialysis.
- An elevated serum creatinine.
- Presence of pre-existing liver disease.

The overall prognosis for purely cholestatic injury is better than that for hepatocellular injury, although fatalities have been reported in the former.

Drug-induced acute steatosis (fatty degeneration) is uncommon and occurs less often than chronic steatosis. Jaundice is usually mild, and serum aminotransferases are lower than they are in cytotoxic injury. Although the biochemical features generally do not appear to be as severe as those seen in hepatocellular disease, the illness can be severe with high mortality

PROGNOSIS

- Chronic liver injury

Chronic injury generally resolves upon discontinuation of the offending drug, but this pattern of liver injury may progress to cirrhosis and liver failure. Cholestasis can be prolonged, requiring several months (>3 months) to resolve. A progression to chronic disease is reported to occur in approximately 5 to 10 percent of adverse drug reactions and is more common among the cholestatic/mixed types of injury.

- Gradual progression to cirrhosis can be seen without any manifestation of clinical illness (as with amiodarone, methotrexate, or methyldopa). Once cirrhosis is established, the clinical manifestations are typical of those seen with cirrhosis from other causes

- Some patients with chronic cholestasis develop vanishing bile duct syndrome.
- In this setting, prolonged damage leads to the loss of bile ducts and overt ductopenia. In rare cases, a progression to cirrhosis and ultimately liver failure results.

PREVENTION

- Preventing drug-induced liver injury (DILI) includes educating patients taking hepatotoxic drugs (eg, acetaminophen) on their safe use, including appropriate dosing and potential interactions with other drugs or alcohol. Patients should also be warned about signs and symptoms associated with hepatic injury. Whether to monitor for DILI by checking alanine aminotransferase (ALT) levels during treatment with a known hepatotoxin is controversial. In some cases acute liver failure has developed in patients who were undergoing screening, and the significance of mild ALT elevations is not always clear and may lead to inappropriate discontinuation of a needed medication. Our approach is to monitor the ALT level in patients taking medications associated with relatively high incidences of severe liver injury, such as isoniazid and methotrexate.

سطوح پیشگیری

Primordial Prevention

Primary Prevention

Secondary Prevention

Tertiary Prevention

Quaternary Prevention

Primordial Prevention

- فرهنگ سازی مناسب جهت جلوگیری از مصرف خودسرانه داروها
- هشدار به مردم در مورد بی عارضه نبودن داروهای گیاهی مرسوم
- هشدار به مردم در مورد عواقب عدم مصرف دوز صحیح داروهای بدون نسخه مثل استامینوفن
- ارزیابی مواد دارویی برای شناسایی خطرات توکسیسیته در ترایال های بالینی

Primary Prevention

- جلوگیری از تجویز داروها بدون اندیکاسیون توسط پزشکان
- توجه به تداخلات دارویی و عوارض داروها هنگام تجویز
- آموزش صحیح مصرف دوز صحیح داروها به بیماران به مدت محدود
- جلوگیری از تحویل داروها بدون نسخه به بیماران در سطح داروخانه ها

Secondary Prevention

- غر بالگری و پایش آزمابشات در بیماران مصرف کننده داروها با متابولیسم کبدی طبق گایدلاین ها
- هشدار علائم و نشانه های بیماری های کبدی به بیماران مصرف کننده داروهای با آثار کبدی

Tertiary Prevention

- پایش متوالی سیر عوارض کبدی با آزمایشات بیوشیمیایی
- مشاوره کبد و پیوند در صورت پیشرفت بیماری به سمت نارسایی کبدی

Quaternary Prevention

- عدم قطع داروهای ضروری بیمار در موارد افزایش غیر significant آنزیم های کبدی
- دادن فرصت کافی جهت ریکاوری فانکشن کبدی به بیماران آسیب دیده

نقش پزشک خانواده