به نام خدا

فارماکوویژیلانس و عوارض ناخواسته داروها

دی ماه ۱۳۹۳

Drug Induced Liver Disease

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- The most causes of drug remarketing in the world
- The number of drugs associated with ADR involving the liver is extensive
- Drugs account for about 10% of patients hospitalized for elevated liver enzyme (except alcohol)
- There are no specific diagnostic tests for drug induced liver disease

Risk factors

- Preexisting liver disease
- Gender
- **Age**
- Genetic factors
- Enzyme inducers
- Alcohol
- Multi drug regimens
- Other diseases
- Nutrition's status

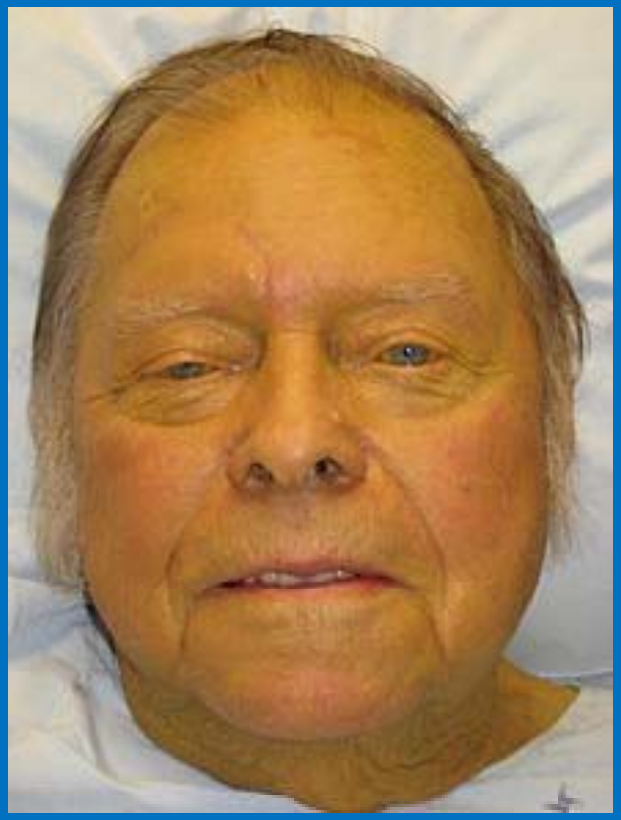
Typical signs & symptoms

Non specific symptoms

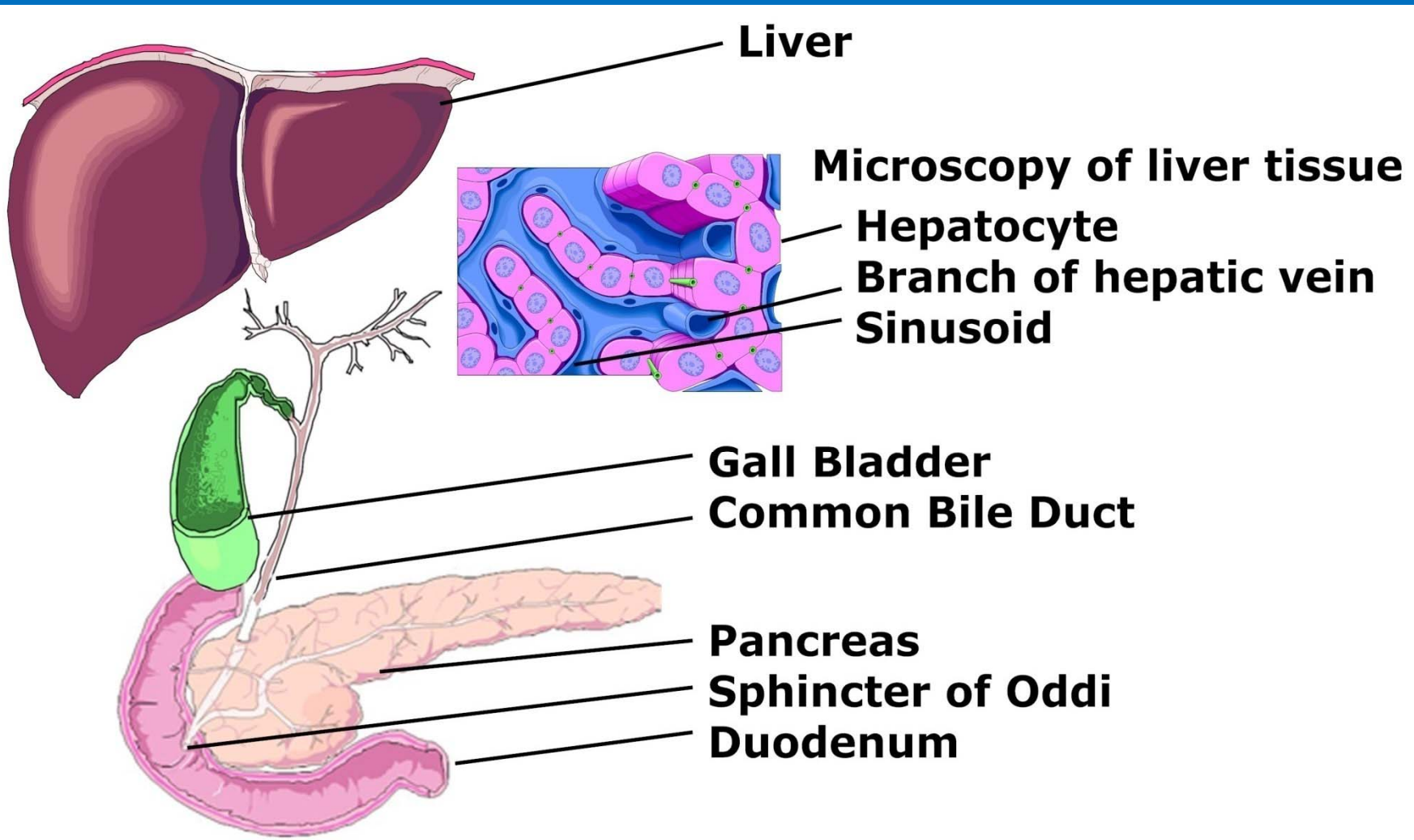
Hepatomegaly

Pain in RUQ & jaundice signs

Puriritus



PATTERNS OF DRUG INDUCED LIVER DISEASE


Liver
Microscopy of liver tissue
Hepatocyte
Branch of hepatic vein
Sinusoid
Gall Bladder
Common Bile Duct
Pancreas
Sphincter of Oddi
Duodenum

Hepatocellular Injury

- Hepatocellular injury is characterized by significant elevations in the aminotransferases which usually precede elevations in total bilirubin levels and alkaline phosphatase levels
- Most injuries occur within 1 year of initiating the offending agent

Cholestatic Injury

- Definition

- Prototype drug: chlorpromazine
- Other phenothiazines,Erythromycin, Captopril, Lisinopril, Amoxicillin-clavulanic acid, Carbamazepin

- Primary involves the bile canalicular system
- Cholestatic disease is more often seen in patients over the age of 60 and is slightly more common in males
- The inability of the liver to remove bile causes intrahepatic accumulation of toxic bile acids

Acute:

- cholestasis with or without hepatitis
- cholestasis with bile duct injury

Chronic:

- vanishing bile duct syndrome
- sclerosing cholangitis
- cholelithiasis

- Most common form of drug-induced cholestasis: cholestasis with hepatitis
- Most patients with this acute disorder present with nausea,malaise, jaundice, and pruritus
- Elevations in serum alkaline phosphatase levels are more prominent and usually precede the elevations of other liver enzymes in serum

MIXED HEPATOCELLULAR AND CHOLESTATIC INJURY

- Combination previous two patterns
- In some patients, an injury may begin as hepatocellular (or cholestatic) and simply spread so rapidly that by the time the patient presents for diagnosis and treatment, all areas of the liver are affected

Liver tumors

- Rare

- OCPs
- Danazole
- Anabolic stroids

Diagnosis of Drug induced Liver Toxicity

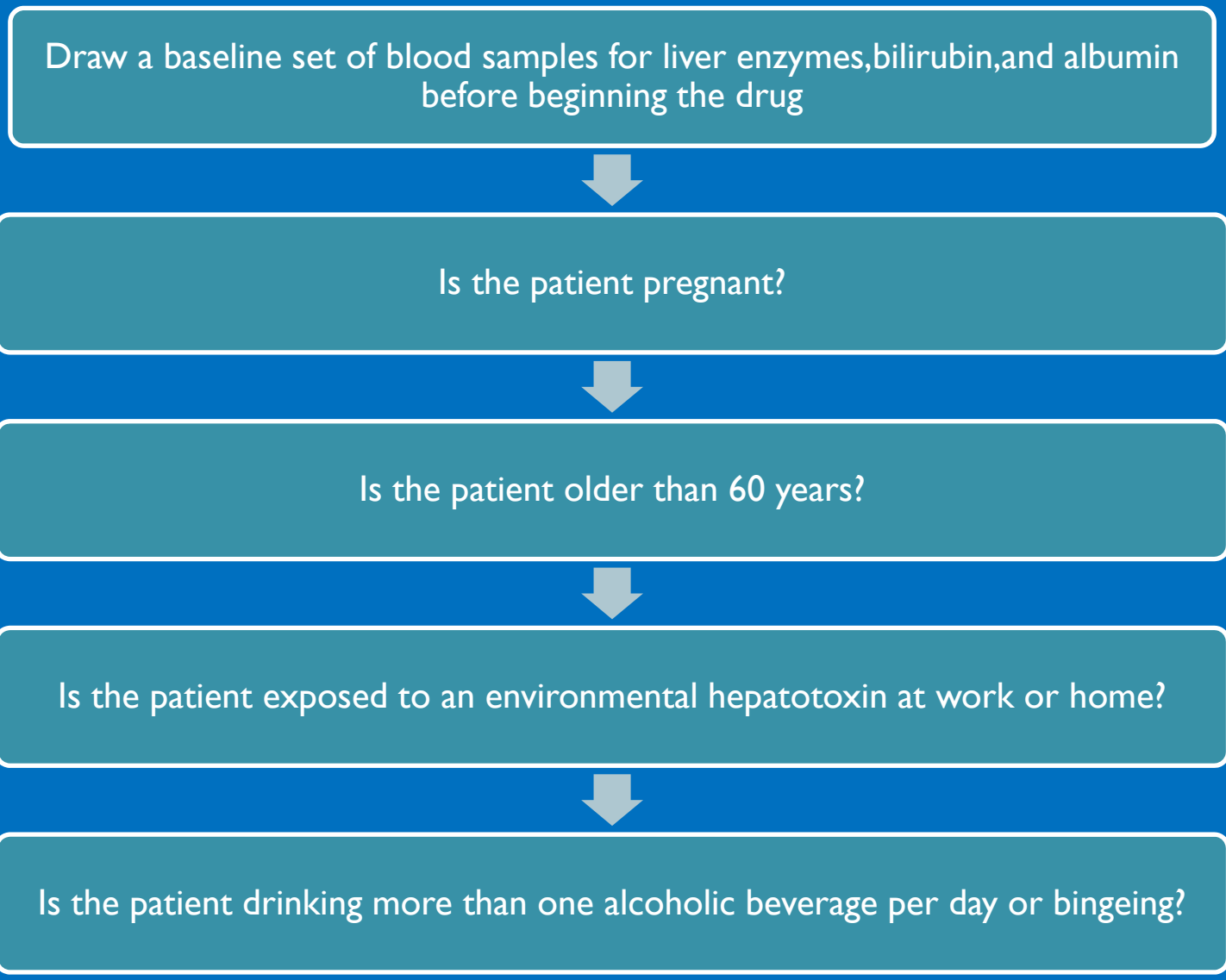
- Drug Exposure
- Onset of abnormality
- Resolution of abnormality
- Clinical features
- Exclusion of other causes

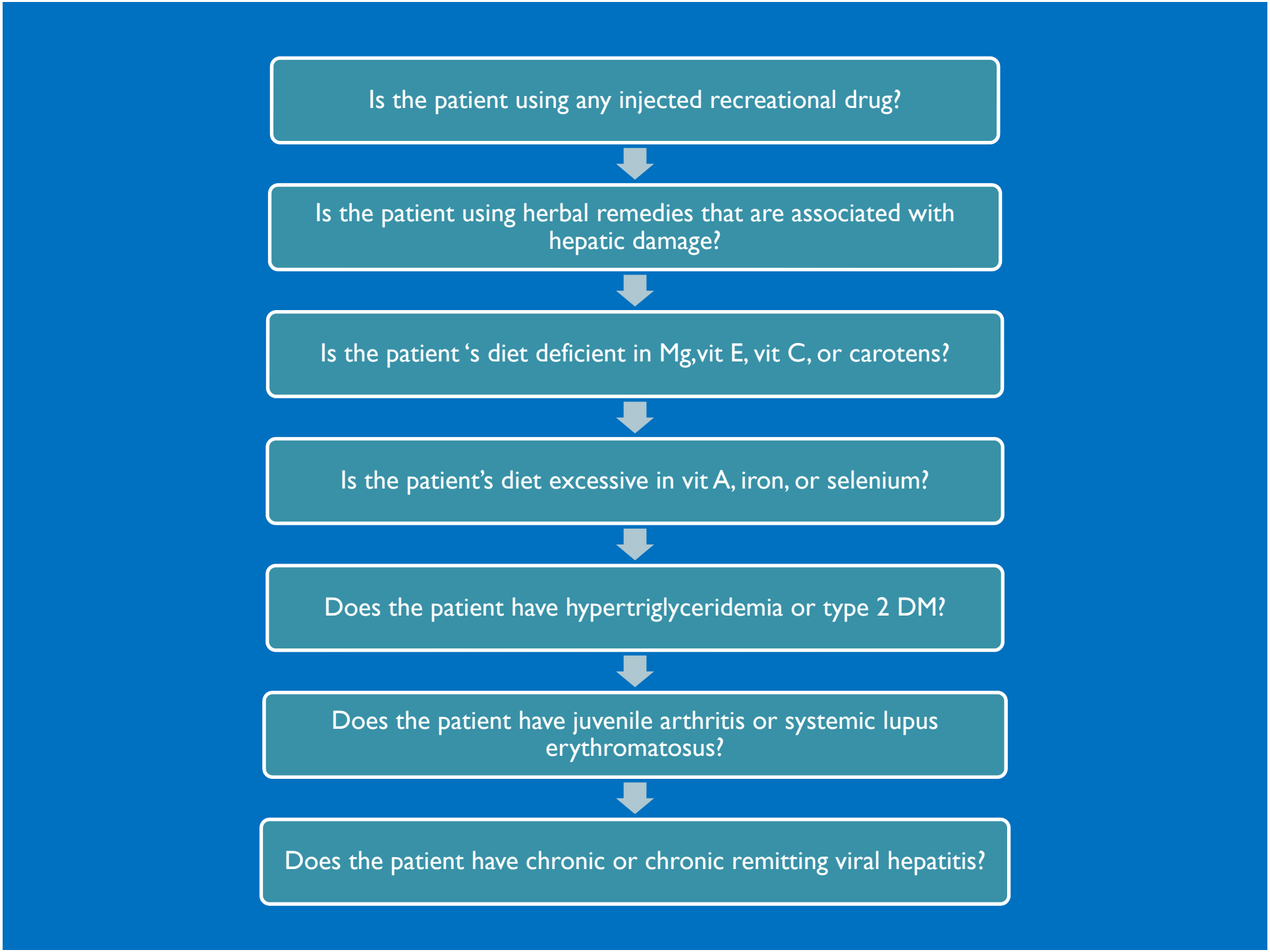
TABLE 40–1 An Approach to Evaluating a Suspected Hepatotoxic Reaction Using a Clinical Diagnostic Scale

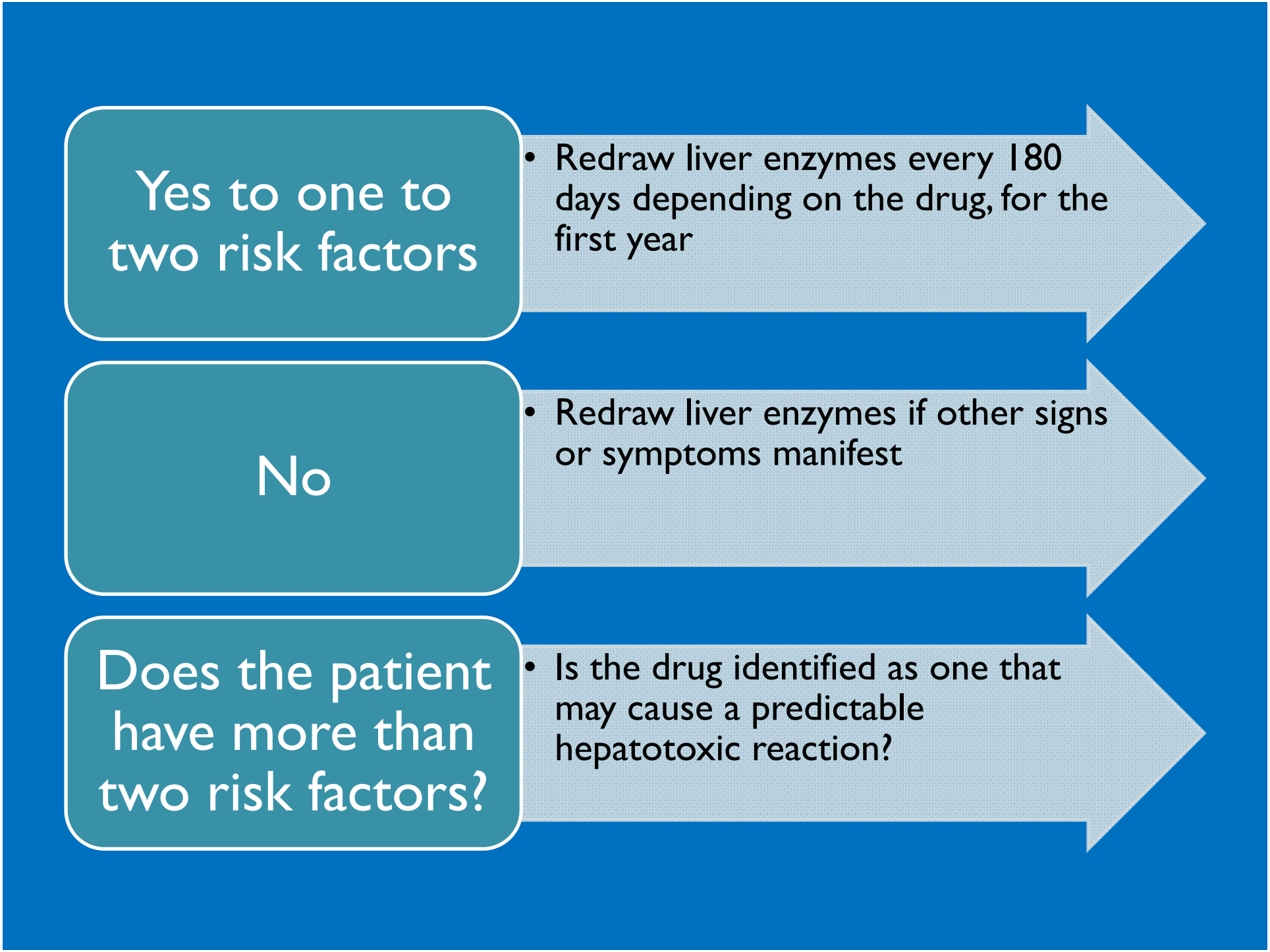
Patient Presents with Elevated Liver Enzymes	Score	Component Subscore
Literature		
Literature supports this drug (drug combination) and pattern of liver enzyme elevation	+2	
No literature supports this, but the drug has been on the market less than 5 years	+0	—
No literature supports this and the drug has been on the market for 5 years or more	−3	
Alternative causes		
Alternative causes (e.g., viral, alcohol) are completely ruled out	+3	
Alternative causes are partially ruled out	+0	—
Alternative causes cannot be ruled out and are possible or even probable	−1	
Presentation		
The presentation includes 4 or more extrahepatic (fever, malaise, etc.) symptoms	+3	
The presentation includes 2–3 extrahepatic symptoms	+2	—
The presentation includes only 1 identifiable extrahepatic symptom	+1	
The presentation is essentially a laboratory abnormality, with no extrahepatic symptoms	+0	
Temporality		
Initiation of drug therapy to onset is 4–56 days	+3	
Initiation of drug therapy to onset is <4 or >56 days	+1	
Discontinuance of therapy to onset is 0–7 days	+3	—
Discontinuance of therapy to onset is 8–15 days	+0	
Discontinuance of therapy to onset is >15 days	−1	
Rechallenge		
Rechallenge was positive	+3	—
Rechallenge was negative or not attempted	+0	
Total Score		—

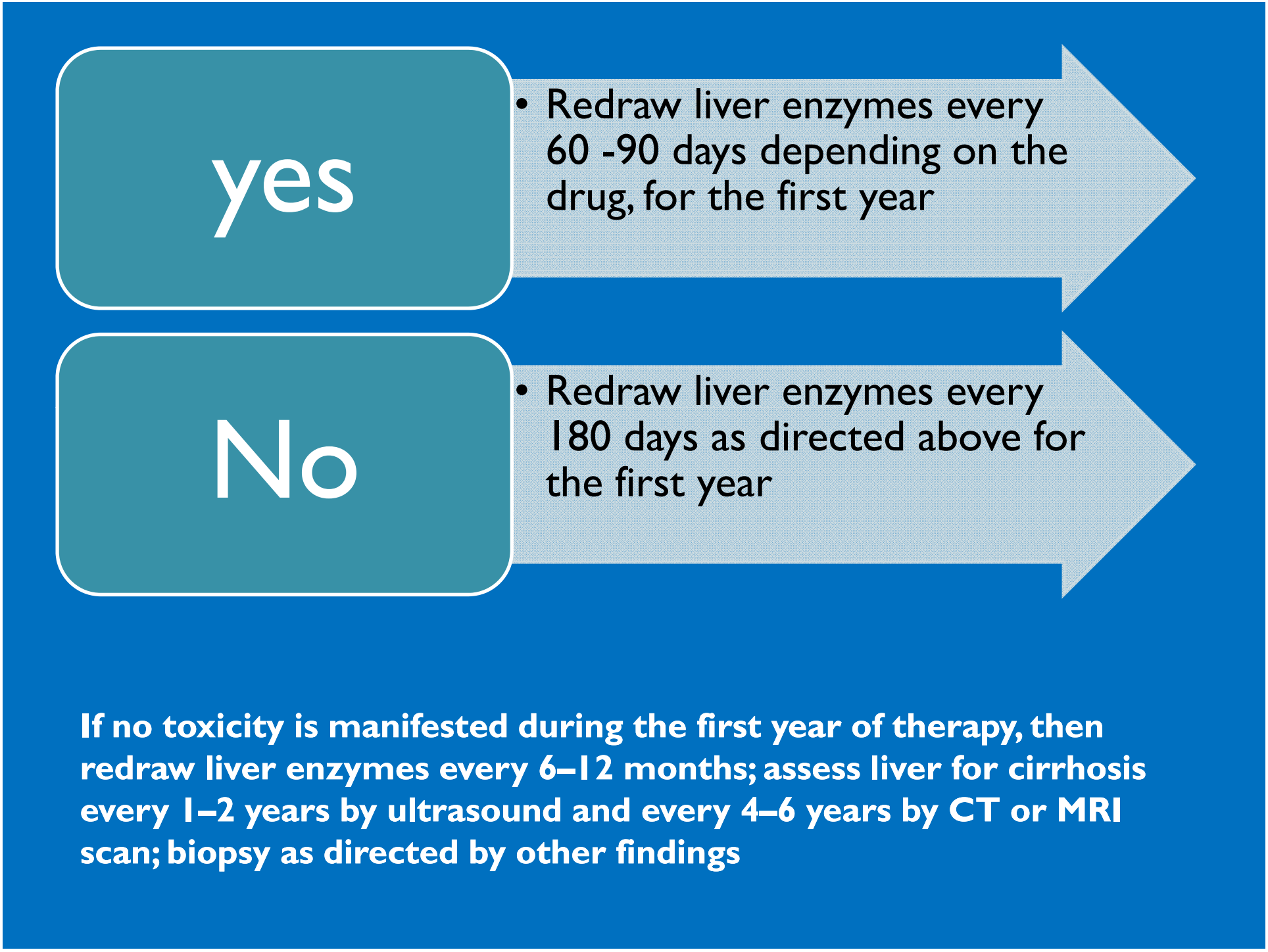
Monitoring

An Approach to Determining a Drug-Monitoring Plan to Detect Hepatotoxicity




Is the patient using any injected recreational drug?
Is the patient using herbal remedies that are associated with hepatic damage?
Is the patient 's diet deficient in Mg,vit E, vit C, or carotens?
Is the patient's diet excessive in vit A, iron, or selenium?
Does the patient have hypertriglyceridemia or type 2 DM?
Does the patient have juvenile arthritis or systemic lupus erythromatosus?
Does the patient have chronic or chronic remitting viral hepatitis?


Yes to one to two risk factors
• Redraw liver enzymes every 180 days depending on the drug, for the first year
No
• Redraw liver enzymes if other signs or symptoms manifest
Does the patient have more than two risk factors?
• Is the drug identified as one that may cause a predictable hepatotoxic reaction?



If no toxicity is manifested during the first year of therapy, then redraw liver enzymes every 6–12 months; assess liver for cirrhosis every 1–2 years by ultrasound and every 4–6 years by CT or MRI scan; biopsy as directed by other findings

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Drug- and herb-induced liver injury: A case series from a single center

LIVER

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ABSTRACT

Background/Aims: Drug-induced liver injury (DILI) is common worldwide and has a potentially fatal outcome. It accounts for more than half of the cases of acute liver failure in the United States. Herb-induced liver injury (HILI) is a less documented condition but a growing problem. We present here the clinical characteristics and outcome of patients with drug- and herb-induced liver injury from our center.

Materials and Methods: In this 4-year retrospective study, 82 patients in whom there was a causal or highly probable relationship between herbal medicine or drug use and liver disease are presented.

Results: The mean age of patients was 43.1±14.8 years; sexual distribution was 53 females and 29 males. The major cause of hepatotoxicity was drugs (87.8%), with herbal medicine accounting for 12.2%. The leading causative agents were nonsteroidal anti-inflammatory drugs (NSAIDs) (23.1%), followed by antibiotics (19.5%). The pattern of hepatotoxicity was hepatocellular in 35 patients (42.6%), mixed in 28 (34.1%), and cholestatic in 19 patients (23.1%). Teucrium polium (known popularly as felty germander), which is a traditionally used herbal medicine of the Labiatae family in our region, was the most common cause of herb-induced liver injury and responsible in 7 of 10 herbal hepatotoxic cases. Acute liver failure developed in 3 patients (two patients related with flurbiprofen and diclofenac and one patient due to an isoniazid-rifampicin combination).

Conclusion: Antibiotics and NSAIDs were the most common etiologic agents for drug-induced liver injury. Surprisingly, herbs follow these groups of drugs and must be questioned more carefully.

Keywords: Drug, herbal preparation, toxicity, hepatitis

Treatment

- Withdrawal of offending drug
- Increase removing of drugs from the body
- Corticostroids
- UDCA
- Supportive cares

Table 7.7 Some drugs for which regular monitoring of liver function tests is recommended

Drug	*LFT monitoring recommended (in UK)*
Amiodarone	Monitor LFTs (particularly transaminases) at baseline and then every 6 months
Cyproterone	Check baseline LFTs and then recheck if symptoms develop
Dantrolene	Check baseline LFTs and repeat 6 weeks after starting therapy
Leflunomide	Check baseline LFTs and repeat periodically thereafter
Methotrexate	Check baseline LFTs, then every 2–3 months
Methyldopa	Check baseline LFTs, then at intervals during first 6–12 weeks of treatment
Nevirapine	Check baseline LFTs then every 2 weeks during first 2 months of treatment, at the third month and then on a 3–6-monthly basis
Rifampicin	In patients with pre-existing liver disease or if pretreatment LFTs abnormal, LFTs should be checked weekly for the first 2 weeks then at 2–4-week intervals
Rosiglitazone	Check baseline LFTs then repeat every 2 months for the first 12 months, and periodically thereafter
Sodium valproate	Check baseline LFTs and repeat periodically during first 6 months of therapy
Statins	Check baseline LFTs and check periodically after that (e.g. every 6–12 months)
Sulfasalazine	As for methotrexate

THE END