[MUSIC PLAYING]

KAPIL CHOPRA, MD: So I'm going to kick off this course with the topic of abnormal liver function tests. To be very honest, this is a huge topic, and I think to do justice, I'm going to try and touch on some of the important areas. And I think the rest of the day, truly, will give you further details into some of these additional disease states that I'm going to address briefly.

So the term liver function tests, it's kind of drilled into us, you know, from med school, LFTs, it's a very commonly used term. However, if you really drill down to liver function test-- and I'll show you what we mean by conventional liver function test-- this is truly an imprecise term. Because most of the tests that we do to test the functions of the liver are really not direct measures of its function. And the other kind of caveat here is many of these tests that we conventionally talk about, LFTs, could be abnormal even in patients with a healthy liver.

So this is our conventional checklist for LFTs, you have the liver enzymes, ALT, a AST, alk phos. I like to put GGT in that list, though it's not in the conventional insurance panel of liver function tests. But it's a very useful test when you have to differentiate the causes of cholestasis or high alk phos. Bilirubin is part of that. And then the true test of liver synthetic function are the serum albumin, and the prothrombin time.

So how do patients come to light? I'm a liver doctor, I'm a hepatologist, and clearly I would only see patients that have been screened by one of you, or colleagues in the primary care setting, et cetera. So it's fair to say that when these quote, "abnormal" LFTs are detected, patients have no symptoms. A lot of these as screening panels, comprehensive metabolic panels, you apply for health insurance, you apply for disability insurance, et cetera, et cetera. These are screening panels done, and out pop up these abnormal LFTs, and that prompts a referral to a specialist.

Hence, the true clinical significance is variable, and it's fair to say that you can reassure your patients that serious underlying liver disease is going to be rare or uncommon. And if you look at the epidemiology-- and I'll show you some data-- clearly there's a huge variation in the prevalence of what I would call significant liver disease, and it all depends on the population under study. And then clearly-- you know, I get this question a lot from my primary care colleagues-- how much should I chase this? Because the patient truly is doing very well, and clearly the degree to which you seek a cause is going to lead to the cause of the problem.

So if you look at population-based studies, and this is a door to door survey, the enhanced database. It's a very elegant database maintained by the NIH. And you know, anyone can access this to analyze different types of data. So if you look at all comers in the US, the incidence of abnormal liver function tests is about 10%. That's the take-home figure to remember.

And if you take out people who are hepatitis C positive, or who had excess alcohol consumption, this would go down to about 80%. So roughly 8% to 10% of the US population will have this quote, "abnorrmal LFTs". And some predictors that indicate an abnormal LFT would be obesity, increased BMI, clearly alcohol use, male sex. There's an ethnic preponderance among the Mexican American, and then clearly younger, and then the HIV positive patients.

Now let's look at some of the other data sets that are available out there. So if you look at 20,000 Air Force trainees, you know, cause for abnormal LFT is 12, 12 out of 20,000. So clearly it's a very subset individual population that we are studying. And then look at the smattering of causes out there, hepatitis B, C, et cetera.

Let's look at a more kind of day-to-day patient population, 100 consecutive blood donors. You can see alcohol use is about half of the causes for the abnormal LFT. Fatty liver, which we talked about briefly, which is nonalcoholic fatty liver, and then hepatitis C. And then again, 10% have no known cause.

And then if you go and look at people who had liver biopsies, again, you can see fatty liver-- whether it's alcohol or non-alcohol-- is always going to be more than half the causes, and then a smattering of some of the other causes that I listed below. So I think it's fair to say you can establish the diagnosis, pretty much noninvasively in most patients. And clearly how far you chase this depends on the pre-test probability, and I'll show you some data of what I mean by that.

At the end of a day, when you really don't know, it's unclear diagnosis after history, lab test, et cetera. And I hate to put this the way I put it, but most will turn out to be alcoholic liver disease, fatty liver, which is nonalcoholic fatty liver. I think alcoholic liver disease is probably one of the most difficult diseases, sometimes. to diagnose.

So how does one proceed in a day-to-day situation. I think whenever you get a lab value of a high ALT, AST, et cetera, the first step is confirm the result. Because a lot of times that sample is just lying before it reaches the lab, and if the blood hemolyzes, you're going to get false positive results. So confirm that. If it's still abnormal, then you can go and see how abnormal is it abnormal.

So minor elevations, and we always look at, what is the upper limit of normal, and be careful, every lab has a different normal. And, you know, over the last 20 years, my head kind of spins, what is normal ALT? You know, 40, 37, 60. So be careful what's the upper number for the lab that you use.

Less than two times normal may not be clinically important if you really ruled out some of the major causes. And this is because, how did we come up with this normal-- you know, what is normal ALT? And you know this is a very sensitive topic for discussion. Because clearly there will be some individuals who fall outside this normal range but are still normal. And truly today, at least in the US, we have not adjusted these different values for sex, and body mass index.

So clearly females will have lower ALTs, people who are smaller, with lower BMIs, will have lower ALT levels. And then, of course, physiologic elevations, and the classic example is a high alkaline phosphatase, which can occur during pregnancy.

So this is just a quick checklist, and you have all these slides sets in your handouts, I'm not going to spend too much time. But you need a good history. So alcohol use, obesity, diabetes, and what I've listed on the left side are some of the clinical history taking that you would do in an office-based setting. Delve into medications, because you'd be surprised how often you can unearth prescription, or even over-the-counter stuff that the patient may be taking, and that could really be the answer for the abnormal LFT.

You want to see what the duration is. I mean, we truly don't chase something that's recent, and in the liver world, you know, the difference between acute and chronic is six months. So anything that's been abnormal for more than six months is probably going to be more significant. And then some of the symptoms, which are rare. Clearly if you have symptoms, it's easy, but as I said earlier, most of these patients are asymptomatic.

Go into the history for potential exposures, transfusions, IV drug use, intranasal drug use, et cetera, a travel history, exposure to people, and then some of the occupational exposures listed there. Do a full clinical exam, I mean, this is all stigmata of chronic liver disease. And again, this only occurs when the liver disease is already advanced. So in practice you may not see any of this. Again, this is the signs and symptoms of advanced liver disease.

When things don't add up. So this is a case I've encountered on rounds in Montefiore a few years ago. A 35-year-old state trooper, he was actually transferred to our hospital, and you know, he had this confusing pattern of abnormal liver tests. He had acute pancreatitis, he had a platelet count of like 20,000 or 30,000. So here I am on rounds, I have two fellows, four medical students, two residents.

And the state trooper tells me, Doc, can you just let these guys wait outside? I need to share something with you. I said OK, I told my team to please step out. And he said, you know, four days ago, I had my birthday, and I was taken out to the bar. And I consumed, you know, my friends gave me these 18 jager bombs over a period of three hours, and I just passed out.

And here I am looking blank, you know, I had never heard of a jager bomb.

[LAUGHTER]

So I said what is a jager bomb? And he looked at me, as if, you know, you need to know, Doc.

[LAUGHTER]

So I went out of the room, I Googled this, and this is what it is. Jager bomb is a cocktail, it's a German brew, it's a German liqueur, Jagermeister. Until today, you know, I think the Germans are very secretive of what they do.

[LAUGHTER]

I do not know what Jagermeister contains, you know, if someone can tell me. But this combination is what he had had. What I'm trying to get at is, I mean, our patients are taking stuff, and when things don't add up-- I mean, this is my take on it-- this could be something the patient did that he or she is not willing to share with you.

So moving on to, I'm going to say, a textbook approach, which we don't see in practice, but it's worth to go through this exercise. Whenever you see these abnormal LFTs, quickly try and sort out which bucket you can put the patient in. Is it hepatocellular, is it cholestatic, or it's a mixed pattern? Now, how do we define this?

Predominant hepatocellular is is when the ALT and AST are more than five times the upper limit of normal. So if normal is 40, more than 200. You can also have a high alk phos, but what you're allowed is two or three times the upper normal. On the other hand, predominant cholestatic is when the alk phos is about three to five times the upper limit of normal, and the ALT, AST will be abnormal, but less than five times normal.

Now, the other thing is, how high are these tests? And it's kind of useful to go through this, and these are three kind of minor, moderate, and major. Clearly the causes are very different for each of these. And I'm not going to dwell on too much on this topic because elevated alkaline phosphotase is a very different kind of topic by itself.

And you know, the causes sometimes are surgical, et cetera. So for the sake of the next few minutes, I'm going to restrict my discussion on elevated aminotransferases, and chronic, meaning more than six month's duration. And we're going to use that cutoff as mild, which means less than 250.

Now I think in clinical practice, I'll show you an algorithm which you can follow, but a lot of times it may be more convenient, especially at tertiary centers. So when a patient arrives at a tertiary center, we combine a lot of tests. But it wouldn't be unreasonable to use a stepwise approach, which you can always change depending on the pretest probability.

So let's go through the stepwise approach, because a lot of the experts in the field have kind of proposed this as a reasonable, quote, "cost effective" way of proceeding. So go through a good medication history, supplements-- meaning over-the-counter stuff-- assess for alcohol use. And whatever questionnaire, whatever tool you have in your office, I think you need to standardize.

You test next for hepatitis, meaning hepatitis B and C, you test for iron overload, and then you assess for fatty liver. I mean it says test for fatty liver, which we can talk about. So this is step one. If you don't find anything on that step, then you flip over, this could be not liver disease. Because you kind of ruled out all the common liver problems.

And this is uncommon, but again, I mean, a high ALT or a high AST could be a muscle problem. Thyroid disease, celiac disease, OK? The thyroid issue is so important, I can't tell you. Probably one or two cases a year-- this is just my practice-- I would pick up uncontrolled or undiagnosed hypothyroidism, that can manifest as an ALT and AST for the first time. Celiac is now well-known as the cause.

If you've ruled out all that, you flip back to the liver, step three. Because now these are rare liver diseases that you're going to kind of screen for. And all of these have screening tests, there's a screening test for autoimmune hepatitis, Wilson's et cetera. And you're probably going to hear more about these topics a little later this morning.

And lastly, you've done everything, and you still haven't kind of reached-- I have to admit, a liver biopsy is our gold standard. However, having said that, you see some data now, you know, noninvasive ways of assessing, especially fibrosis, and you may be able to circumvent the biopsy. I mean, I like the referral that I get, the patient comes to my office, and it's kind of prepared that I'm probably going to order the biopsy. So a lot of our primary care docs, our colleagues in the community, GI docs, would prepare the patient, you're probably going to have the biopsy when you see the liver doc.

So going through some of these causes in more detail. As I said, I'm not going to dwell on too much of these causes, because you have some very elegant talks later this morning on probably each of these. So drug-induced liver injury-- very common, and virtually any drug can do this, I think this is just a short list out there. What I would like to highlight here is herbal stuff, because that's where we don't pick up easily.

The history is the key. And again, the timing of the drug injection to the abnormal liver tests is always important to establish. And it could be an old drug that they were taking for a while, but when a second drug, or a third drug is added, the toxicity of drug number one goes up. So just because they were on Lipitor at dose x for all these years, doesn't mean the statin can't do it, because when a second or a third drug was added, the toxicity of drug a went up.

Clearly alcoholism contributes to some of these drug-induced liver injuries. So some of the features that suggest the drug-induced liver injury, I mean, the patient was previously well. Clearly the timing of the abnormal LFT, stopping the drug. A lot of times in practice, the drug will already be stopped by the time you see the patient, and if things get better, it's a fairly simple diagnosis.

And sometimes, not always, we would actually go to a liver biopsy. The problem is there's no liver biopsy signature that kind of tells you this is drug a or drug b. And a lot of these liver biopsy findings are kind of nonspecific. Alcohol, as I said earlier, sometimes very difficult to establish, especially on visit one, and you may need to delve back into the history.

Whatever questionnaire you choose to develop, you can in your practice. That ratio mentioned over there is useful, so clearly the AST to ALT ratio, whether its two to one, three to one, increases the probability. And clearly, that altered ratio can also be seen in patients with NASH and advanced NASH or hepatitis C, and already established cirrhosis.

You know, a lot of times I ask the patient, so how much alcohol do you consume? And he said Doctor, social. And I think that's not a good enough answer. So You have to delve deeper, because people's conception of how much alcohol is excess is very, very variable. So what I put out there is that is what we define in the US-- and this is more for studies-- as to what a standard drink is. And this is based on the amount of alcohol, the alcohol content of each of these different alcoholic beverages.

So how much alcohol is excess? I get this question a lot. And believe me, and what I'm going to share with you. When I was a med student, and I read my first textbook of liver disease, written by Dame Sheila Sherlock, what was considered excess alcohol use was more than 80 grams of alcohol for a male, and 60 for a female. Which, in other ways of saying this, you could go up to eight drinks a day for a male, and six drinks a day for a female.

Look where we've come down to. So this is the most recent quote, "definition" of excess alcohol use. So clearly females are more susceptible than men, and in women it's now down to one, and men, less than two. So I think, again, these are definitions used in studies, but it's a very useful definition to use in practice. And as I said, no amount of alcohol is safe as far as a liver doctor's concerned.

So alcoholic liver disease is an interesting entity, because it's reversible if intervention takes place at the right time. And I kind of use this in the clinic a lot, to talk to patients. Because clearly, you know, if you go from normal to fatty liver, to steatohepatitis, it's still reversible if the patient stops drinking at stage three. But clearly, once you have fibrosis, once you have cirrhosis, that becomes an irreversible state of liver disease.

We talked about the ALT, AST, the elevated GGT may be helpful. And then clearly it's rare for the AST to be very high. So clearly AST levels that are more than four or five times elevation, it could be alcohol, but it could be alcohol plus something else.

Hepatitis C, just one slide. I think you're going to hear much more a little later. Screening-- this is a recent recommendation-- baby boomer screening, and I'm not going to dwell too much on this right now. You're going to hear much more by the next speaker.

Hepatitis B, what's new. Again, you're going to hear much more about this a little later. I think the pretest probability is very important here. I mean, who would you really want to screen hepatitis B? Clearly people who are immigrating from parts of the world with a high disease prevalance, which I'll show you in a second. And the new thing here is-- this is more for our colleagues in hematology-- because re-activation can occur when patients who receive these therapies, like retuximab, et cetera.

So our GI colleagues, our hematology colleagues have caught on to this, where they start screening for hepatitis B, when they start using these drugs to prevent re-activation. This is the, map, so to say different parts of the world have higher incidence of hepatitis B. So clearly, with immigration occurring today, I mean, people originating from parts of the world with high seroprevalance need to be screened.

You need to use the right tests. I can't tell you how many times I see a patient, and it's a funny combination. I use the word funny because you can start with the surface antigen, clearly you add a surface antibody, and a core antibody, IgT or total. You need all those three, that's how we take decisions based on what to do, and what not to do. And then, of course, that different combinations of tests. And you're going to hear more about hepatitis B a little later today.

Last disease, which is probably becoming the most common liver disease today in the United States, nonalcoholic fatty liver disease. Again, a lot more to come later today, but you know, it's not a new problem. I mean, we've known about this for decades. But clearly, today I think it's going to probably account for the most common cause of chronic liver disease in what we see.

Risk factors are listed there, metabolic syndrome, the clue may be the AST/ALT ratio. And that's there's no test today for this entity. You know, it's a history, it's risk factors, and then you can do other ancillary techniques to support the presence of fat. You can use radiology, ultrasound, CT, or MRI. And finally, the liver biopsy.

So as I said, it's not a new problem, we've known about this for years. And you know, it's alcohol-like liver disease in individuals who do not consume excess alcohol. It's a spectrum out there, you can have fat alone, so steatosis, you can have fat plus inflammation, so steatohepatitis. And then obviously this disease can progress to cirrhosis. As I said, it's mainly a diagnosis of exclusion.

Today 30%-- depending on which study you look at-- but 30% of the US population probably has nonalcoholic fatty liver disease. And this is how it progresses-- fat, fat plus inflammation, and then cirrhosis. And once you have cirrhosis, the patient is at risk for the standard complications of cirrhosis, liver cancer, et cetera.

So we talked about the spectrum, and clearly fat alone has a different prognosis as opposed to fat plus inflammation. And you can see there, again, a very useful slide when you talk to patients. Because if it's fat alone, I mean, the risk of progression to cirrhosis over a decade is less than 5%. On the other hand, if you have fat plus inflammation, the risk of progression to cirrhosis is almost 30% over that decade.

And the problem here is you need a biopsy to sort out fat, versus fat plus inflammation. And a lot of us don't do biopsies for these patients. So hopefully the noninvasive techniques will help us. Why does this disease happen? We still don't know. You're going to hear more about this, natural history, a little later. Treatment is again, treatment of metabolic syndrome. And ultimately, if you see a patient that's already has cirrhosis, you need a new liver. You need transplantation.

And it's fair to say that the on the index biopsy, that means even when you see the patient for the first time, almost 10%, 15% already have established cirrhosis. We see this from our bariatric surgery colleagues, because patients go for bypass, or gastric bypass surgery, unknown whether they had liver disease or not. The surgeon opens the abdomen, patient already has cirrhosis. Usually most of our surgeons do not proceed further, and that prompts a referral to us. So, almost 15% may have established cirrhosis at the outset.

So I'm going to end on a few slides. Who to observe. Clearly, if it's less than 2 times, you could probably sit on that for a while. And as I said, our standard cutoff is six months. I mean, if I see a patient-- or sometimes, patients already come to us, they've waited six months-- but I don't mind waiting six months. I would go a little longer sometimes, if it's less elevations.

Clearly chronic liver disease can be identified by noninvasive testing, and it's not unreasonable to keep following these patients, which means a little bit of patience. I mean, you have to reassure the patient that you're not really missing anything major. You can introduce lifestyle measures, take out the drug that may be implicated, et cetera. And expectant follow-up may be a reasonable approach. Some of these patients will get better and you may not need invasive tests.

So expectant follow-up is the most cost effective strategy for patients who are asymptomatic, and have negative tests for viral metabolic autoimmune markers. And this was based on a study published in *Gastro.* On the other hand-- and I don't mind admitting, and I'm probably guilty of this-- because by the time a patient reaches a tertiary center, this is in our hand, we tend to biopsy more often than not.

And who would I biopsy? Again, people in whom the ALT/AST are more than two times, and persistently elevated. And then it comes back to, Doctor, what are you going to see in my biopsy? I get this question a lot. And I answer the question both ways.

I think I'm not just necessarily looking for a problem always. You know, even if that biopsy turns out to be vague, nonspecific, et cetera, it's very reassuring for both patient and physician to know that we've ruled out a serious problem. Because this is the term I use in the clinic, liver disease is unforgiving. And what do I mean by that?

I mean, it's very easy when the patient has advanced disease to diagnose probably any liver disease. But today, and I say today, because this may change over time, I mean, our therapies are not able to reverse fibrosis, and I say that today, because this may change. So once you have advanced fibrosis, once you have advanced liver disease, it's easy to make the diagnosis, but you cannot reverse the process.

And again, these probably are not true for diseases like hepatitis B, maybe C, and some of the newer therapies that may be coming down the pipeline. So just a quick smattering, if you went ahead and did a liver biopsy, what really did it-- how did it change our management? And you can see it probably changed the diagnosis in about five patients, it changed the treatment, about two patients.

And again, what did we see? nonalcoholic fatty liver, one third, fatty liver, probably alcohol, another one third, and then some smattering over there. So again, it just supports that notion of a 10% having no known cause. And then again, the same thing over here.

Today we have noninvasive tools for assessment of liver fibrosis. And again, you're going to hear more about the applications of this technique, it's a very useful technique called-- the principle being elastography. The machine that we have FDA approved is now called the Fibroscan, it's done at the bedside. It's a very useful tool for assessment of fibrosis. So not for etiology, but for assessing severity of liver disease, it's a great tool, and actually the biggest application probably would be in follow-up with patients.