[MUSIC PLAYING]

SHAHID MALIK: I'm Dr. Shahid Malik, so I'm going to be talking about another controversial indication for liver transplant, which is alcoholic hepatitis. So I want to start with a case that we just saw last week on service. So 25-year-old white female, lives with her boyfriend. She started drinking about 10 years ago. Currently drinking about a half gallon of vodka daily.

She's had three DUIs in the past. She's had DTs. She was recently fired from her job. Per the psych notes on admission, she realizes she has an alcohol problem that's ruining her life and her family's life, and she desperately wants to quit.

She's a pack per day smoker. She's experimented with cocaine in the past, but not currently using. She reports significant anxiety and difficulty with sleep.

She had a suicide attempt 10 years ago-- overdosed on pills. She was previously on anti-depressants and anxiolytics. She was seeing a psychologist up until about a year and a half ago. Notably, her father had an alcohol use disorder and committed suicide at the age of 25.

She lives with her boyfriend and her boyfriend's two teenage children. She was educated. She had a four-year degree in finance and was about to start a job as a manager at a restaurant. She has a healthy mom who's 45 and a 14-year-old brother.

So the patient was hospitalized at a local hospital for eight days in January of this year for hepatitis. Her bilirubin, at that time, was normal, but the other labs were very consistent with alcoholic hepatitis. Her ultrasound showed fatty liver. She was instructed to stop drinking. She now presents to our hospital with two weeks of nausea, vomiting, and generally just not feeling well.

On exam, her BMI was 25. Her heart rate was 100. She was tremulous, but awake. She had deep jaundice, numerous spider angiomata, carotid enlargement. Her liver was massively enlarged with an audible bruit, and she had mild lower extremity edema.

Her labs were notable for hyponatremia and renal failure. Her bilirubin, which 12 weeks ago was one, was now up to 20. Her INR was 2.2. Her white count was 15. Her alcohol was positive on admission at 195.

Her viral serologies were negative, and this is her CT scan. So massive hepatomegaly occupying more than 80% of her cavity. You can see the left lateral segment actually hooking her spleen over on the left side. It was profoundly fatty infiltrated.

So Hounsfield units are a measure of density, and typically, a normal liver runs between 50 and 75 Hounsfield units. Hers was negative 28, which is indicative of severe fatty infiltration. She was pan cultured, which was negative. EGD showed small varices.

So my first question to the audience is, what would you recommend? We can just take a vote, maybe by hands. Would anyone treat this patient with steroids? Discharge home and follow up with Ramone?

[AUDIENCE LAUGHING]

AUDIENCE: That's never the wrong--

SHAHID MALIK: That's never the wrong answer. Follow up with Dr. Malik is always the wrong answer. Palliative consult? In-patient site consult? Liver assist device?

Trental? Deceased liver transplant? Liver biopsy? Suweta, we know you're going to vote for the next one. Relax.

Live donor liver transplant? So the mother is begging to be a donor. Or neupogen? So we'll come back to this.

So acute severe alcoholic hepatitis is an acute manifestation occurring from healthy-- or heavy alcohol ingestion. There are histological criterion, but for the most part, the diagnosis is made on clinical grounds-- fever, jaundice, AST greater than ALT, abdominal pain, tender hepatic megaly. A hepatic bruit on exam is actually pathognomic for the disease.

The severity of alcoholic hepatitis is historically based on laboratory criterion. So traditionally, we use the discriminate function, which is a calculation which takes into account the bilirubin and INR, and a score of greater than 32 is defined as severe disease. Or the MELD score, greater than 20.

The most important thing from this slide is the short term mortality in this disease is about 50%, so half of patients will be dead at three months. And this is another important point-- although the presentation is acute, the disease itself, almost exclusively, is the manifestation of heavy chronic alcohol use in the setting of very advanced liver fibrosis, so almost akin to an acute-on-chronic liver failure.

So this was the proudest moment of my life. Not necessarily that I had a kid, but the fact that-- look at where this stethoscope is placed. This stethoscope is instinctively placed in the right upper quadrant. So she's listening to see if her younger baby has a bruit. She did not.

But this took a lot of work. This was a lot of years of honing to get this baby to be a future hepatologist. I took her to the GI lab. I even had her introduced to Dr. Starzl.

So the other day, I was on call, and I came back, and there was a little bit of blood on my scrubs. And Safa, who's my daughter, now six, she was asking, what happened? Why is there blood?

So I pushed it a little too far, and I sat her down, and I showed her a variceal bleed on YouTube. She almost passed out. And now, she tells me she no longer wants to be a hepatologist. She wants to be a princess slash art teacher.

So the baby who's sitting behind her, I've completely given up on. She wants to be Supergirl slash Michael Jordan. This picture took me 10 minutes, and she was like, dad, my arms are getting tired. But I finally got it.

So the treatment of alcoholic hepatitis-- so of course, the cornerstone of therapy, is lifelong abstinence. The medical therapy of alcoholic hepatitis, historically speaking, has not been great, and recently, has been called into question. So this was probably the end-all-be-all of trials for alcoholic hepatitis published four years ago in the *New England Journal.*

So 1,100 patients with a clinical diagnosis-- it was not biopsy proven in all cases. Diagnosed with acute severe hepatitis. They were randomized to one of four groups-- so placebo; trental, which we've been using for quite some time; steroids; and then a combination of trental and steroids. Primary endpoint was mortality at one, three, and 12 months.

Like most patients with alcohol, majority were male-- 65%. Median age was 48. The mean MELD score was 21. So the patient population that we're going to be talking about a little bit later, patients that may require a liver transplant, are usually a little bit sicker. But this will give us some idea about the medical therapy.

I just wanted to give a shout out to Dr. Sheik, who was someone who taught me about alcoholic hepatitis. His sentinel paper is now approaching 20 years, believe it or not. This is the trental paper published in *Gastro,* approaching an incredible 1,000 citations, but this paper has kind of done away with trental, and perhaps even steroids.

So this paper showed a trend towards statistically significant mortality benefit at 30 days for steroids, but none at longer follow up. And even more so than that, there were serious infections in about 13% of patients treated with steroids versus 7% of those who did not. And at least, my experience, my use of steroids has probably declined by about 75% since the onset of this paper.

Other things have been looked at for the treatment of alcoholic hepatitis, including a liver assist device. I only wanted to show you this paper because I was an author on it. It was negative, but I also wanted to show it so I could use this slide.

Sounds good. Doesn't work. Sounds good. Doesn't work.

So what about liver transplant for alcoholic liver disease in general, meaning a decompensated alcoholic cirrhosis? So like most transplant studies, the sentinel paper was written by Dr. Starzl. There was Dr. Toto next to him. So this was published in 1988 in *JAMA.* Dr. Van Thiel and Dr. Marsh were co-authors.

So it showed 71% one-year outcome. Returned to alcohol in this relatively small study of 40 patients was infrequent-- only two patients. But follow up was relatively small.

So this is very interesting. So this is an NIH consensus conference from 1983, so five years prior to that paper. And they mentioned, in this paper, that alcoholic liver cirrhosis and alcoholic hepatitis-- so incredibly enough, alcoholic hepatitis was mentioned originally when it came to transplant. So patients who have established clinical indicators for fatal outcome and who are judged likely to abstain from alcohol may be candidates for transplantation.

They concluded that only a small proportion would be expected to meet these rigorous criteria. So this makes several assumptions. Number one, it implies that we have some means of predicting relapse in this patient population. And number two, importantly, it implies that it is appropriate to deny those deemed high risk for relapse.

So how good are we at predicting a relapse? So Ramone's is going to be talking about this a little bit in the next talk, but it varies. It seems to be anywhere from 10% to 30% in all comers, all patients undergoing liver transplant for alcohol, whether that's chronic cirrhosis or acute alcoholic hepatitis. Importantly, going back to drinking does seem to impact patient survival. Based on this study in 2015, you can see the five-year survival in patients who remain abstinent is pretty good, 80%, but drops to about 50% in patients who go back to drinking.

This is also another important point. Initially, in 1983, they said only a small proportion would be expected to meet these rigorous criteria, and that's no longer the case. Alcoholic liver disease has become the most common indication for liver transplant in the United States. Very good one in five year survivals, however.

So this was that paper. You can see the indications for liver transplant are changing. So just nine years ago, 30% of patients were transplanted for hepatitis C. With the DAAs, that's declining rapidly-- now 18%. And alcohol and fatty liver are quickly becoming the number one and two indications.

So I was kind of finishing up fellowship, ready to start my career, when the DAAs came, and I was incredibly nervous. I was like, oh, my god, I'm not going have a job. Hepatitis C is gone. But thank god for America.

So this is not important, but it's interesting. So if you look at Boston Beer Company over the last five years, their stock prices have gone from 200 to 335. McDonald's has gone from 100 to 200. And Gilead, which makes Harvoni and the more popular Hep C drugs, has actually declined from 120 to 60. So just kind of a snapshot of our landscape when it comes to the most common diseases we see in our liver clinic.

So this is a paper published in August 2017. Alcohol use disorder has increased by nearly 50% in the last 10 years. In certain groups, it's rose even higher, and some of these are incredible. So in women, 84% increase; African-Americans, 93%. And this took me for surprise-- in patients greater than the age of 65, over the last 10 years, alcohol use disorder, which has a very strict definition, has increased by well over 100%.

So when it comes to alcohol and liver transplant, almost all centers transplant patients with decompensated alcoholic cirrhosis. Most centers and insurance companies do require, however, a six month rule. But this rule is not set in stone, and by no means is a contraindication to liver transplant. So let's talk a little bit about the six month rule.

Although it was mentioned in the initial 1983 statement, liver transplant as a therapy in patients with acute severe alcoholic hepatitis, for many years, was considered beyond the pale. A survey of liver transplant centers in 1996 reported 85% of programs required at least six months abstinence, and the thought was this would allow patients time to recover from the acute insult, and as a surrogate for recidivism. So this essentially excluded patients with alcoholic hepatitis, historically.

But from the beginning, experts in addiction medicine have not been supportive of the six month rule. For example, studies suggest, especially in male patients, abstinence was secured only after five years, and many experts recommend a more nuanced approach, using other factors to determine whether or not a patient is going to go back to drinking. But this formed the impetus behind the French study, which I will talk about.

So given the dismal prognosis in patients with acute severe alcoholic hepatitis, poor overall medical therapy, and the lack of consensus regarding the six month rule laid the foundation for the landmark French-Belgian trial, which was published in the *New England Journal* eight years ago, already cited nearly 500 times. So seven liver transplant centers-- in the end, it only ended up being 26 patients with severe alcoholic hepatitis, not responding to medical therapy, essentially steroids, with a discriminate function greater than 32. The inclusion were pretty strict.

So I kind of summarized it here, but it's more extensive than this. But generally speaking, no prior liver decompensation, so you could not have presented with a prior bout of alcoholic hepatitis or ascities or something like that. You had to have supportive family members. There had to be a commitment to abstinence, and then there had to be a complete consensus amongst the relevant providers or transplant team.

These patients were pretty sick. The mean MELD score was 34. And this is the outcome of the study, and it was-- I think all of us knew what it was going to show, but to see it in black and white is pretty dramatic. So medical therapy in patients with severe alcoholic hepatitis-- survival was only 24% at six months versus those transplanted. It was 78%. And I would challenge you to find another intervention where you would see such a dramatic response in a sick patient population.

The two-year follow up showed about three out of 20 patients-- six patients were lost to follow up-- of the survivors returned to some alcohol use without impacting graft survival. The important point here is that this was highly selective. Of all the patients that they initially considered, less than 2% of patients admitted with alcoholic hepatitis eventually were transplanted, and the centers only used about 2.9% of their available liver grafts for this indication.

So again, I want to stress this-- importantly, less than 2% of patients admitted with alcoholic hepatitis were eventually transplanted. Do you want me to say it again? I will. Less than 2% of patients admitted with alc-hep were eventually transplanted.

So the study did have immediate impact. 97% of practitioners, at least in Europe, now consider alcohol hepatitis as an indication for liver transplant. 71% of French centers are now performing liver transplant for alc-hep, and nearly half of centers have reduced the duration of their six month rule.

The US experience has been a little bit more hesitant. So this is a 12 Center Consortium retrospective study. A lot more patients, though-- 147, transplanted between 2006 and 2017.

Very similar demographics. Very sick patients. Mean MELD was 40.

Interestingly, this is a little bit of a side note, only 59% had evidence of alcoholic hepatitis on explant, and that may be an argument that maybe we should be biopsying these patients. But the results are difficult to argue with. The one year survival in this population-- remember, the mean MELD was approaching 40-- was 94%. Three year survival was also very respectable at 84%. 25% of patients did have some relapse into alcohol, 11% deemed harmful use.

So now 25% of centers in the US are performing liver transplant for alcoholic hepatitis. A majority, however, greater than 80%, have only performed a handful. So every Tuesday, we meet at 3 o'clock to discuss patients that should be listed for liver transplant, and over the last one year, a fair number of these have been patients with alcohol hepatitis. I took a picture from one of our listing meetings. This is how they go a lot of times.

So let's talk a little bit about arguments in favor of liver transplant for alcoholic hepatitis. So number one, liver transplant saves lives in this patient population. I think that's undeniable with the studies I just showed you. The six month rule is imprecise and discriminates against potential good candidates.

Three, a majority, upwards of 80% of the public surveyed, demonstrates neutrality, at least neutrality in regards to liver transplant for this patient population. And alcohol use disorder is a disease with a complex genetic, psychologic, and social foundation. And remember, personal behavior influences a lot of the diseases that we see.

Arguments against liver transplant for alcoholic hepatitis-- number one, a required interval of abstinence, at least six months, allows for liver recovery, and this is definitely true. You're going to end up-- if you're doing a lot of transplants in these patients, you're going to end up transplanting patients that eventually would have gotten better. Not a large amount, but some.

Two, a required interval of abstinence allows patients to demonstrate a commitment to abstinence. Three, public perception for liver transplant is negative, and it will lead to a reduced organ donation. Four, alcohol is a self-inflicted condition, and these patients are less deserving. Five, transplantation of patients with alc-hep in greater numbers will lead to more recipients with post liver transplant alcohol relapse and, potentially, greater rates of graft loss.

The most common that I hear on the floors and in between rooms and stuff is this one-- alc-hep is self-inflicted condition. You just have to remember-- liver disease, probably more so than any specialty in all of medicine, is based on habits and making poor decisions. So it's a slippery slope, I think, when you're going to start judging individual patients that we take care of. Ultimately, we're in this job to save lives, but that being said, there does remain significant controversy regarding liver transplant for alc-hep.

Number one, it's definitely a limited resource. In essence, you're taking away an organ from the donor pool. Two, as I mentioned, this is a self-inflicted disease. Three, alcoholics, generally speaking, are not always honest with regards to their consumption, and that can lead to significant frustration in caring for these patients.

Four, the severity of the disease, many times, pushes patients to the front of the transplant list, and this is something I struggle with probably the most. In other words, some of these patients come in. You only know them for a few days. They get listed, they get transplanted, and then in your clinic, you're seeing patients for-- that are struggling with chronic liver disease for months, if not years, waiting to get transplanted. And that does perhaps seem a little bit unfair.

So although not addressing all of these issues-- so I want to talk about live donor for liver transplant, mainly for three reasons. Number one, I'm contractually obligated to mention live donor liver transplant. Number two, every time I mention live donor liver transplant, I get $10 onto my salary. And number three, if I don't mention live donor liver transplant, I will get a constant barrage of texts from Dr. Ganesh, and if all of you know Dr. Ganesh, you want to stay away from that.

So incredibly enough, there's not a lot of data on this. The only medium sized study I could see was out of India, published in July 2018. So 39 patients who did not respond to medical therapy-- they compared them to historical controls, so 461 live donor liver transplants. Very similar criterion in terms of family support. No psych contraindications.

Diagnosis was based on clinical grounds and explant review. These patients were not nearly as sick as some of the other studies. The mean MELD was 22, but the outcomes, again, were respectable. 28 month survival was 84%. Again, there was a relapse of 30% in this group.

So we've been doing transplant for alc-hep now for about a year. We see a lot of alcohol in Pittsburgh. I just did a MARS search of alcoholic hepatitis, so these are individual patients within the UPMC system in the last year-- 478. That's not scientific. Not all of them are going to have severe disease, but I would say we average, on week, at least three to five patients with severe alc-hep. We've put nine patients through a full evaluation and, ultimately, have transplanted six, all with deceased liver transplant.

So it goes without saying that liver transplant for acute severe alc-hep is not a solution to this global epidemic. I would be remiss if we didn't talk about some of the staggering numbers related to alcohol. So 88,000 deaths per year attributed, in America alone, to alcohol. 3.3 million worldwide. Alcohol is the leading cause of death worldwide in patients aged 15 to 49.

Every 51 minutes in the US, someone dies of an alcohol related motor vehicle accident. 700,000 students between the ages of 18 and 24 were assaulted yearly related to drinking. 36% of individuals incarcerated for any reason were drinking at the time of their offense.

The cost of excess alcohol-- this is in 2010, so significantly outdated-- was $250 billion. Alcohol ads have increased by 400% over the last 40 years. The World Health Organization stated that nearly 200 diseases are comorbid with the consumption of alcohol, and the average child will be exposed to 1,000 alcohol advertisements per year.

And this was a stunning recommendation made by the European Association of the study of liver diseases. Look at their point number two. Advertising and marketing of alcohol, either directly or indirectly, should be banned. Pretty remarkable statement, but seems to make sense.

This was a large study that gained a lot of national attention, published in *The Lancet* looking at the burden of alcohol use basically worldwide, 195 countries, and you can read the statement there. There is compelling and urgent need to overhaul policies to encourage either lowering people's levels of alcohol consumption or abstaining entirely. The myth that one or two drinks a day are good for you is just that-- a myth. This study shatters that myth. Our results show that the safest level of alcohol or drinking is none.

So I had to show this. So the prevalence of alcohol use-- that should be use, alcohol use worldwide. So Denmark has the highest, with 97%. The main reason I'm showing this, though, is the lowest prevalence is Pakistan. So Pakistan is number one in nothing in the entire world when it comes to anything, so I'm proud to show that Pakistan has the least amount of drinking.

AUDIENCE: They don't report it.

SHAHID MALIK: What's-- they don't report it. Yeah, I don't know. So take home points that are not debatable-- number one, the prognosis in patients with acute severe alc-hep who do not respond to medical therapy is dismal. Number two, the medical therapy in patients with alcoholic hepatitis is of dubious efficacy.

Three, liver transplant for selected patients with alcoholic hepatitis has far superior outcomes to medical therapy and undoubtedly saves lives. Four, liver transplant for alcohol hepatitis, of course, is not a cure. And five, return to alcohol leads to worse outcomes post liver transplant.

Take home points that are perhaps debatable-- some of these are my opinion. Number one, a large transplant center should offer liver transplant in selected patients with alcoholic hepatitis. Two, the criterion of patients who are to be evaluated for transplant must be consistent. Three, the initial screener should be stringent, so this is a very high resource patient population not only from a medical standpoint in terms of sickness, but from a cost standpoint and from a morale standpoint.

Number four, only a fraction of patients will or should eventually make it to transplant. This is number five. Ultimately, no matter what criterion you apply, up to one third of patients will return to some type of alcohol use.

Number six, liver transplant for alc-hep is not a cure, of course, and post liver transplant rehab is imperative. Six, with new liver allocation rules, patients with alc-hep, especially those with high MELDs, as inherently they do, may benefit the most. And lastly, small studies suggest that live donor liver transplant for patients with alc-hep have good outcomes.

As with any new indication for liver transplant, a learning curve for candidate selection is expected, and we're still searching for that malign criterion that we use in HCC for liver transplants for alc-hep. In conclusion, liver transplant for alcoholic hepatitis has evolved from being a taboo in the early era of liver transplant, to become an emerging and effective rescue therapy for highly selected patients with severe disease not responding to medical therapy. Further studies are warranted.

So lastly, I grew up in Pottsville, Pennsylvania, which is about an hour and a half from Philly, four and a half hours from Pittsburgh. Pottsville is famous for two things, and two things only. Number one, it was a big coal mining city back in the day. Number two, of course, as all of you know, it's the home of Yuengling Beer, which is the irony in all of this.

So incredibly enough, I grew up on the same street as the brewery. It hasn't changed in 200 years. Every one and every thing in Pottsville drinks.

So I debated, should I end this talk in a funny joke? And I said, no, I'm not because this is not funny. I'm going to close by showing you the last slide of the case, which is tragic.

I've been seeing these patients for 15 years. This is the second youngest patient I've seen who succumbed to the disease. That 25-year-old developed hepatorenal syndrome, a variceal bleed. She was banded, but continued to deteriorate, and eventually was made CMO.

She's survived by her 48-year-old mother and her 14-year-old brother. So that's all. Any questions, more than happy to take them.