ACG Guidelines for the diagnosis and management of DILI

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Thank you, John. Nice commentary there. I don't have a formal disclaimer conflict slide that we do for CME, but I do want to disclose I think I am a boring speaker, I think.

The American College of Gastroenterology commissioned this practice guideline in 2012. It took about two years to write. It was published in June 2014 in American Journal of Gastroenterology. Most of the authors are from the drug-induced liver injury network (DILIN) which, as many of you know, is the group chaired by Paul Watkins, and Jose Serrano is the Program Officer from at NIH.

It is an interesting story. There have been stories all morning, so I will tell you a story as well. I belong to the group that identifies topics and assigns authors for these Practice Guidelines. One morning the meeting was in Vegas. I was late. Too much poker the night before. This guideline writing was assigned to me. (Laughter.)
Some of you may have worked on practice guidelines. They are not easy to write; they need a lot of consensus-building, compromises, and the society leaders have their own opinions, et cetera. So, it is not an easy thing to do. Skip Hayashi was the second author on the practice guideline, and he is here, with Vic Navarro, Will Lee, and Bob Fontana, who also have done wonderful work.
Practice guidelines use different elements to attribute the strength of the recommendation as well as the quality of evidence. As you will see in this guideline, the quality of the evidence ranged anywhere from low to very low. Basically, the editors asked, "Show us the papers. If you cannot show us the papers supporting what you are saying, it doesn't matter how strongly you feel. It just has to be low or very low evidence." That is what it came down to. And the strength of the recommendation is clinically how strong they feel, whether it is a strong recommendation or a conditional recommendation.

So, the practice guideline had a number of summary statements and recommendations made that I will review. These are about 16 of them. Let me just walk through. Some are pretty straightforward. I would like highlight some that seem very strong, common-sense recommendations, a no-brainer, and yet, you will see a very low level of evidence, just simply because there are no published data supporting that.

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<th>Strength of Recommendation</th>
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<td>Strong</td>
<td>Factors influencing the strength of the recommendation included the quality of the evidence, presumed patient-important outcomes, and cost</td>
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<td>Conditional</td>
<td>Variability in preferences and values, or more uncertainty. Recommendation is made with less certainty, higher cost or resource consumption</td>
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<th>Quality of Evidence</th>
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<td>Moderate</td>
<td>Further research may change confidence in the estimate of the clinical effect</td>
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<td>Low</td>
<td>Further research is very likely to impact confidence on the estimate of clinical effect</td>
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<td>Very Low</td>
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The first recommendation was about patients with suspected hepatocellular or mixed DILI. Acute viral hepatitis and autoimmune hepatitis should be excluded with standard serologies and HCV RNA testing. I think what made it to the practice guideline is hepatitis C RNA testing. In some industry case report forms, you see hep C RNA, but in the clinical setting it is not being done. They just do an antibody, which can be falsely negative. And in the DILIN prospective study we incorporated hep C RNA, but it has not been done on a consistent basis.

There was a lot of debate about anti-hep E IgM testing. I think in the DILIN prospective study there were about seven cases early on that Tim Davern was the first author in the gastro paper where, for all purposes, the cases looked like DILI. When you dug deeper, when Bob Purcell at NIH did the serologies, there were about seven cases that were potentially acute hepatitis E. But one of the reasons that did not make it to the practice guideline is there is not a commercially-available test. Once again, keep this in mind. This is for practicing clinicians, not for researchers. So, here we could not recommend routine anti-hep E IgM testing, just for the lack of there is no standardized testing. But, as you work up in the drug development Phase 2/Phase 3, if you see it, I think it is important to consider hep E IgM.

Whereas, acute CMV, acute EBV, acute herpes simplex are based on clinical scenarios, if there are, for example, lymphadenopathy, atypical lymphocytes, then you test for these. Finally, Wilson’s disease and Budd-Chiari are also on a case-by-case basis rather than on all-comers. And again, really low to very low level of evidence.
Imaging did not make it. It is done a lot in the clinic. Just about everybody with DILI gets a liver ultrasound or a CT, even for AST like 9500, generally speaking, overused. But in the practice guideline for hepatocellular and mixed DILI there is no imaging required, whatever it is worth for industry investigators here.
For suspected cholestatic DILI, I think abdominal imaging is pretty straightforward to exclude DILI pathology. And I cannot tell you how important it is. Sometimes you may even want to repeat it few weeks later, especially if alkaline phosphatase is continuing to go up or bilirubin, because I think early on we did not see dilated bile ducts two weeks later that showed up, but there were cases of pancreatic cancer picked in DILIN prospective study where we enrolled based on early ultrasound that was negative. Serological testing for PBC should be limited to selected cases. And MRCP or MRI—excuse me—MRCP should be quite limited as well, although in clinical practice this is, once again, quite more utilized.
When to consider a liver biopsy? Dr. Kleiner is sitting in the audience; he has published really wonderful papers recently in this area. Biopsy is optional. So, a lot of low level of evidence, which just generally means this is a lot of consensus and expert opinions rather than published studies. A liver biopsy should be considered if you cannot exclude autoimmune hepatitis. I don’t think anyone would disagree, common sense, but, not one rigorously tested. So, I think this was a low level of evidence, especially if you consider immunosuppressive therapy. Liver biopsy may be considered for a number of sub-bullets here. There is an unrelenting rise in liver bile chemistries or signs of worsening liver function, despite stopping the suspected offending agent. (Strong recommendation, very low level of evidence)

- if there is unrelenting rise in liver biochemistries or signs of worsening liver function despite stopping the suspected offending agent. (Strong recommendation, very low level of evidence)

- if peak ALT level has not fallen by > 50% at 30-60 days after onset in cases of hepatocellular DILI, or if peak Alk P has not fallen by >50% at 180 days in cases of cholestatic DILI despite stopping the suspected offending agent. (Conditional recommendation, very low level of evidence)

- in cases of DILI where continued use or re-exposure to the implicated agent is expected. (Strong recommendation, very low level of evidence)

- if liver biochemistry abnormalities persist beyond 180 days to evaluate for the presence of chronic liver diseases and chronic DILI. (Conditional recommendation, very low level of evidence)

And after stopping the compound, if the DILI is not resolving as you would like to, for example, if the ALT has not fallen by 50 percent within a couple of months or, for example, peak alkaline phosphatase has not fallen by 50 percent at six months, to see if the patient is evolving into some form of chronic injury, whether chronic hepatitis or vanishing bile duct syndrome. Especially in chemotherapeutic agents, if you need to re-expose the patient to the same compound. It also happens to some
degree in the IBD area. You need to give the same biologic agent because the patient needs it.

Then, it is a consideration. This more happens with the low levels. A patient may have underlying NASH. In clinical settings sometimes you may not have baseline. If you started a biological agent and you have an ALT of 90 or 100, you don't know if it is a new onset, whether you want to stop. Is it underlying NASH. That is another reason. Obviously, if liver test elevations, after a DILI episode if they are not resolving at 180 days or, actually, I think it may be Bob Fontana's paper will say, after the onset if you have persistent abnormalities, consider a follow-up liver biopsy or consider a biopsy to see if the patient has evolved into chronic DILI.
Recommendations

4. *Re-exposure to a drug thought likely to have caused hepatotoxicity is strongly discouraged, especially if the initial liver injury was associated with significant aminotransferase elevation (for example, > 5xULN, Hy’s law or jaundice). An exception to this recommendation is in cases of life threatening situations where there is no suitable alternative.* (Strong recommendation, Low level of evidence)

5. *In individuals with suspected DILI, especially when liver biochemistries are rising rapidly or there is evidence of liver dysfunction, suspected agent(s) should be promptly stopped.* (Strong recommendation, low level of evidence)

6. *No definitive therapies are available either for idiosyncratic DILI with or without ALF; however, NAC may be considered in adults with early stage ALF, given its good safety profile and some evidence for efficacy in early coma stage patients.* (Conditional recommendation, low level of evidence)

7. *NAC is not recommended for children with severe DILI leading to ALF.* (Strong recommendation, low level of evidence)

Bullet 4, the recommendation that re-exposure is strongly discouraged. This was discussed at many of the meetings here. I think Chris Hunt had some data from Glaxo at the time. Especially if the initial episode was significant I am not using the word "clinically significant" but if the ALT were five times or Hy’s Law, et cetera. Of course, in medicine you cannot always meet case by case. There may be an exception made there is not a suitable alternative.

Recommendation 5, in individuals with suspected DILI, especially when liver biochemistries are rising rapidly or there is evidence of liver function, suspected agents should be stopped promptly. Does anyone disagree? It is a strong recommendation, super-strong, but the evidence is low level.

The sixth is about no definite of three treatments. NAC could not be approved. There was some soft data with acute liver failure, drug-induced in children from Will Lee and Bob Squires. It said not recommended in children, but in adults it is a soft conditional recommendation that drug-induced acute liver failure, NAC could be used because in the NAC trial there was a subgroup that showed benefit, at least a trend towards benefit. So, that was a conditional recommendation with a low level of confidence.
Recommendation 8 was about herbal and dietary supoplements (HDS). We are seeing a lot and this is getting a lot of publicity. Patients should be encouraged - (directed at clinicians and medical monitors in clinical trials) to report the use of HDS, and they should be reminded that the supplements are not scrutinized at the same level or not at all in some instances as drugs. And the diagnostic approach for HDS is sort of evolving. Especially, the difficulty is multiple compounds are taken at the same time. So, it is not easy to attribute to a single compounds. You don't know the signatures. Nonetheless, I think the exclusion, the severity, causality, adjudication issue just generally followed the same guidelines.

Recommendation 10 is straightforward common sense, which is, if you suspect HDS-related DILI, stop the compounds. Once again, low level of evidence.

Recommendation 11 is about DILI in patients with chronic liver disease. Underlying chronic liver disease requires a high index of suspicion. There is a paper from DILIN that is on the MedLine, an early ePub, that describes about a paper that had 900 DILI cases, and about 90 of them have underlying chronic liver disease. It seems like a majority were fatty liver disease. And there is a two-by-two comparison of DILI in patients with and without chronic liver disease. I think if you get a chance, you may want to look at some of those.

But the point is that it is extremely difficult, especially with patients with hep B, hep
C, when they have an increase in ALT or bilirubin, to know if the cause is underlying liver disease, as opposed to what is drug-induced. Keeping high vigilance is desirable.

When you look at the package inserts, especially for many of the compounds, there is frequent biochemical monitoring in patients with underlying liver disease. When you look carefully I know Janssen has written a nice commentary on this as well really you don't find much data supporting that the careful biochemical monitoring prevents, actually, when clinicians follow. In the case of statins, everybody knows less than 50 percent of the providers prescribing statins do the tests in a fashion that was at least early on in the package inserts.
This recommendation reads, "There are no data to recommend specific liver biochemistry monitoring plan when a potentially better toxic agent is prescribed in individuals with known CLD. Often, information contained in the package inserts is incomplete or unhelpful. Patients should be advised to promptly report any new onset symptoms such as yellowing of their eyes, abdominal pain/discomfort, nausea/vomiting, itching or dark urine. Additionally, it is reasonable to monitor serum liver biochemistries at 4-6 weekly intervals, especially during the initial 6 months of treatment with a potentially hepatotoxic agent. (Conditional recommendation, very low level of evidence)"

This recommendation reads, "There are no data to recommend specific liver biochemistry monitoring plan when a potentially better toxic agent is prescribed in patients with known chronic liver disease." This is a big problem, though. Especially if you think about fatty liver as a known chronic liver disease, you are talking a third of U.S. adults. Often the information contained in the package inserts is incomplete or unhelpful. Once again, I think Einar’s commentary in Gastro two or three months ago is quite instructive. For the same compound by two different manufacturers, it might have entirely different recommendations. For example, sumatriptan made by one company would have one instruction, one warning; whereas, made by some other company would be totally different.

Patients should be advised to promptly report any new onset symptoms such as yellowing of their eyes, abdominal discomfort, itching, dark urine. That is pretty straightforward.

We thought it was reasonable to monitor liver biochemistry at four- to six-week intervals, especially during the initial six months of treatment with potentially hepatotoxic agent. A very soft recommendation. This is more so on consensus rather than evidence. That is how this received a Michelin one star. (Laughter.) A really low level of evidence.

So, practice guidelines rest on compromise, expert consensus. Especially in a field
like DILI, there are not a lot of randomized trials.

I am going to stop there. Thank you.