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Management of the Patient with Hepatitis B

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Dr. Nguyen: Hello. I am Mindie Nguyen, Professor of Medicine at Stanford University. Welcome to our program. We hope to help you in identifying patients to screen for hepatitis B, how to evaluate them, how to monitor these patients, and who to treat. And it’s my great pleasure today to introduce my colleague, Dr. Nezam Afdhal, Professor of Medicine at Harvard Medical School.

First, I would like to share a quick summary outline for our program today, the must-know of hepatitis B. Number one is that hepatitis B is a DNA virus; and number two, it has a rich serology. Dr. Afdhal will help us to interpret how to use the serology to diagnose and to stage patients. Number three to note is that the majority of the mortality of hepatitis B is with chronic infection, and not acute infection. Mortality with acute infection is very low, less than 1%. But for chronic infection, most children and infants exposed to hepatitis B remain chronically infected. This is a large reservoir of hepatitis B infections, and this is the focus of our program today, how to prevent these young people to become infected and how to monitor and treat them to prevent long-term complication.

First, I would like to ask Dr. Afdhal to help us on which serology to use to diagnose a patient and to identify who needs to be vaccinated still, and who may reactivate if they’re exposed to chemotherapy or biologics that would suppress the immune system.

Dr. Afdhal: Thank you, Mindie. So as we know, there are approximately two billion people exposed to the hepatitis B virus worldwide and approximately 300 million people who might have chronic infection. The hallmark serologically of chronic infection is a positive hepatitis B surface antigen. This is always present if there’s chronic infection. For there to be active infection, there’s also the presence of a variety of other serological markers. Patients may be hepatitis B e-antigen positive, so-called wild type hepatitis B, usually younger patients, or maybe hepatitis B e-antigen negative. We also measure the hepatitis B viral DNA, which is a marker of active viral replication. Thus, an infected patient is surface antigen positive, maybe e-antigen positive or negative, and DNA positive.

This accounts for the 300 million who have chronic infection, but there are also those that have been exposed. They may have lost surface antigen and they may only have as a marker of prior exposure, antibody to hepatitis B core. They would be DNA negative since there is no active viral replication. These patients, as Mindie suggested, can very rarely reactivate their hepatitis B when exposed to the right environment such as under the severe immunosuppression that occurs with certain oncological treatments. There’s also the inactive carrier state, where one is really not replicating the virus, but is surface antigen positive, usually e-antigen negative, but has no active DNA. These are the viral serological parameters that we look for.

Dr. Nguyen: Thanks Dr. Afdhal. Now, in regards to the natural history of hepatitis B, what would you give as a number, percentage, for a patient just newly diagnosed with hepatitis B, what’s the chance that person may develop liver cancer or die from hepatitis B?

Dr. Afdhal: That’s a very good question and one that all of our patients ask. So, as you so clearly said, most adults who get acute

infection, which is either blood borne or sexually transmitted, 90% of them are able to clear the virus spontaneously. It's really those people that are exposed at a very young age, either at time of birth with vertical transmission from the mother, or as young children who go on to chronic infection, an estimate as high as 90% of those, thus, they've had the disease for a long time. The disease can progress in two different pathways. One is the pathway of cirrhosis, which is scarring of the liver, leading eventually to potentially liver failure, portal hypertension, decompensation and transplantation. And the other way is the progression through oncogenesis. The hepatitis B virus is an oncogenic virus. That means that it can produce cancer, and it produces primary liver cancer or hepatoma and this can occur in 5-10% of chronic hepatitis B infected individuals. So when we think about this, what we really have is a risk that is predetermined by duration of infection, age, male gender, family history. That puts our patients at risk over a long period of time, 40, 50, even 60 years to the development of liver cancer.

Dr. Nguyen: So Dr. Afdhal, once a patient gets diagnosed with a positive surface antigen and we get DNA test, as you mentioned, and we give them counseling, what other tests would you recommend the primary care physicians or gastroenterologists who see the patients the first time do as the ABC minimum?

Dr. Afdhal: Well, I think if you diagnose chronic hepatitis B, it's also important to rule out the other viruses. We always tell people to check for chronic hepatitis C since, especially in adults, they can go through the same pathway of sexual and blood borne transmission. We recommend that patients have hepatitis A antibody checked and if negative are vaccinated for hepatitis A. The delta virus is a virus that is opportunistic in that it requires hepatitis B for its coexistence, and so we recommend a hepatitis B delta antibody in all of our patients. And then finally, if there are any other risk factors, HIV testing is a good thing. So that's the battery of tests for other viruses that we would do.

The next question is what is the risk of the patient developing chronic liver disease through the pathway of inflammation and fibrosis to cirrhosis? And the test that we do for that initially is an ALT test. The ALT will tell us if there's any evidence of activity within the liver and inflammation. Our newer guidelines recommend lower levels of ALT in terms of further evaluation. For women, we take an ALT of 19 and for men an ALT of 25. This is much lower than the standard criteria that we used to use of ALTs of less than 40. So I think it's important for us to recommend that these tests are done in all of the patients and if there's evidence of viral replication and high ALT, consider treatment according to the guidelines.

Dr. Nguyen: So if I see a patient and I check the tests that we just discussed, the patient is e-antigen negative, a man, the FibroScan was done and there was no significant fibrosis detected in FibroScan, and the patient has an ALT of 55, and DNA 120,000, would you recommend to treat now or to monitor? What would you recommend?

Dr. Afdhal: Thank you for giving us such a simple case, Mindie. That patient meets all of the criteria for all of the guidelines – Asia-Pacific, European and U.S. guidelines – for treatment. He's e-negative, viremic with a DNA greater than 2,000 and his ALT is elevated two times the upper limit of normal so absolutely, that's a treatment candidate for treatment with chronic hepatitis B. What's more complicated is the same patient except his ALT is somewhat lower and perhaps even within the normal range. That's a little more complicated and the guidelines vary there with some recommending treatment and others saying follow.

Dr. Nguyen: Technically with the U.S. Algorithm, that patient would meet criteria but by AASLD criteria, the patient's ALT needs to be more than 70 I would treat the patient, too, but technically, it doesn't meet AASLD criteria.

Dr. Nguyen: So thanks, Dr. Afdhal. So if I see the patients and have done the tests as you recommended and found that I have a 49-year-old Asian man, e-antigen negative, DNA 120,000 IU/ml and ALT about 50, would you recommend this patient be treated or be monitored?

Dr. Afdhal: My recommendation is usually for treatment for these patients. The ALT meets the European and Asian guidelines but perhaps not the U.S. guidelines, which require a higher ALT, above 70. However, this patient has active disease and inflammation. Most of our Asian patients are slender and thin, and the upper limit of normal of ALT is somewhere between 25 and 30 for a male, so this is an indication that there is activity ongoing. And, I think that the guidelines really are based on the fact that in the past, treatments were associated with risk of resistance, with intolerable side effects from interferon but today's newer therapies are highly effective, very safe and tolerable, and really have no issues with respect to resistance. So this patient, to me, is an at-risk patient for disease progression and I would recommend treating the patient.

Dr. Nguyen: Thank you.

Dr. Nguyen: So just two more quick bullets; reactivation and pregnancy. So, we discussed the patients with chronic infections and we have many of these patients with chronic or prior infections who may receive biologics or more therapy and nowadays, we see this really often, not just in cancer patients but in dermatology, rheumatology clinic. So what do you recommend? What serology should the doctors order? And which general group of patients should be started on treatment and who we can monitor?

Dr. Afdhal: So it's a very important question. I think most societies now, rheumatological, oncological, realize the importance before using these biologics and/or chemotherapeutics to screen for HBV. The surface antigen is the appropriate initial test. And if treatment is going to be prolonged, the antibody to core. If you have antibody to core, as we said, you have prior exposure, and those patients should be prophylaxed with an oral agent to prevent recurrence. If you have surface antigen present, even without DNA, you absolutely should be prophylaxed with an oral nucleotide or nucleoside to prevent recurrence. This is important because when recurrence does occur in these patients, it tends to be quite a severe recurrence and can have significant associated ALT flare, liver inflammation, and we have even seen cases where this inflammation has led to acute or chronic liver failure and even death. So, very important to screen these patients who are being considered for biological agents or chemotherapeutic agents.

Dr. Nguyen: Thank for the great advice and also especially for mentioning the anti-core antibody testing because for the vast majority we probably could monitor but unless they will take the anti-CD20 or B-cell depleting biologics or stem cell transplantation, then they would be prophylactic too from the get go. But one thing people tend to forget to do is to continue the treatment after the end of the chemo or the biologic treatment for a certain duration, depending on the type of treatment. So I would like to ask you, what is the recommendation for treatment after the end of chemotherapy or biologics?

Dr. Afdhal: So, I don't think there's any absolute duration of therapy that's recommended. I can tell you what I do in practice, and that is if somebody has received a fixed course of chemotherapeutic agent for a cancer, we go on for at least six months and usually 12 months post the cessation of chemotherapy. For the biologics it's a little different because many people either stay on biologics long-term or they get intermittent use biologics and I find it much more difficult to consider a stop time point in those patients.

Dr. Nguyen: Great. My practice is similar, and I also err on the side of being safer and would treat them for 12 months rather than six months because the drugs that we have now for hepatitis B prophylaxis are quite safe. And the same for the biologic, the anti-CD20; they usually stay on it chronically, like you said, or intermittent, so we don't really nave to think about when to stop the hep B medicine. But, sometimes they do stop and in those cases, I usually continue the hep B treatment for at least one to two years because there's a lot of case reports on delayed reactivation in the case of these biologics.

Now, getting to another population that is also pertinent, the younger group of people, the childbearing age woman, if they meet the criteria, do all of them need to be started on antiviral therapy right away, or we can wait until after family planning? And if they get pregnant, what is your threshold on starting antiviral therapy during pregnancy?

Dr. Afdhal: So that's a very complicated question. You know, essentially, I have a discussion individually with every patient about the risks and benefits of treatment in the young. If they have active disease with elevated ALT, e-antigen positive, high viral load, I recommend treatment and I tell them that it's important that if they get pregnant, they need to let us know. I prefer in young patients to use one of the tenofovir based drugs because they are a class B agent in pregnancy, which means that they have been studied and there's been significant pregnancy registries.

The issue of when a patient becomes pregnant and they're on the antiviral is one that again requires discussion because there is a risk of stopping the antiviral and inducing a liver flare versus the potential risk of the antiviral to fetal development. I usually counsel my patients to stay on the antiviral but it really is dependent and different from patient to patient. Breastfeeding, these drugs are excreted in the breast milk and therefore that's another discussion that is required with patients. Complicated but certainly something we think about.

If the patient does not want to go on antiviral therapy early in the pregnancy, then what I usually also do is in the third trimester, at the beginning of their third trimester, perform an HBV DNA test and if the HBV DNA is greater than ten million, I recommend that for the last three months they go on an antiviral agent to prevent transmission to the infant at the time of birth. This has been shown to be effective even when we give all of our infants hepatitis B vaccine and immunoglobulin at birth. Those who are born to patients with a high viral load can still become infected.

Dr. Nguyen: Thank you. That's very helpful for monitoring these patients and counseling. So I find the same; counseling is very important and individual discussion. We are getting close to the end of our time here and I want to end with what I think may be one of the most important first steps to screen and diagnose these patients. After all these years, we've been talking about this for the last two or three decades at least but new data, up to 2016, still show that only about 15% of Americans with hepatitis B have been diagnosed. So, what would be one quick way you could recommend and help all of us practitioners to remember who to screen so that we don't miss the next opportunity we see a patient that should be screened?

Dr. Afdhal: I think this is an area where one does screening in high-risk populations, which are patients who come from areas where HBV is endemic. So I screen all of my Asian patients, including those from China, Vietnam, Cambodia, Laos, Thailand, all of them are screened for hepatitis B. Sub-Saharan Africa is another area in which hepatitis B is endemic and they should all be screened. You know,

what we forget about sometimes is that Eastern Europe also has a high prevalence of HBV and one should also be aware of the risk factors for transmission such as multiple sexual partners, use of intravenous drugs or parenteral exposure. Quite honestly, we're moving towards global screening for hepatitis C of all patients between 18 and 70. Wouldn't it be nice if we thought about the same type of responses for hepatitis B as well?

Dr. Nguyen: Thank you. We are getting to the end of our program here. I would like to thank Dr. Afdhal for all the very helpful and practical recommendations with screening as well as on how to identify patients who may need to be initiated on therapy and to monitor them for liver cancer with ultrasound every six months. Thank you.

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