JOHNS HOPKINS MEDICINE
eLITERATURE REVIEW
eViralHepatitis Review
Jointly provided by the Johns Hopkins University School of Medicine and the Institute for Johns Hopkins Nursing
Supported by educational grants from Gilead Sciences, Inc., Merck & Co., Inc., and AbbVie, Inc.

VOLUME 5 - ISSUE 10

LISTEN TO PODCAST | DOWNLOAD PODCAST | PHYSICIAN POST-TEST | NURSE POST-TEST

Managing DAA Failures in Light of New HCV Regimen Approvals

- Explain the risk of resistance development following unsuccessful HCV therapy with direct acting antivirals.
- Discuss the impact DAA resistance and other negative predictors (for example, cirrhosis) may have on newly the approved retreatment options.
- Describe effective retreatment strategies for patients who have previously failed HCV DAA therapy.

Guest Faculty Disclosure
Dr. Wyles has disclosed that he has served as a consultant and/or advisor to AbbVie, Inc., Gilead Sciences, Inc., and Merck & Co., Inc. He has also received grant and/or research funding from AbbVie, Gilead Sciences, and Merck & Co.

Unlabeled/Unapproved Uses
In his discussion today, Dr. Wyles has indicated that he will make reference to the unlabeled use of ribavirin with the sofosbuvir/velpatasvir/voxilaprevir combination, although such use is recommended in the current HCV treatment guidelines.

MEET THE AUTHOR

David L. Wyles, MD
Chief, Division of Infectious Diseases
Denver Health Medical Center at the University of Colorado
Denver, Colorado

Release Date:
November 30, 2017

Expiration Date:
November 29, 2019

LISTEN TO PODCAST NOW | DOWNLOAD PODCAST | SUBSCRIBE NOW | PHYSICIAN POST-TEST | NURSE POST-TEST

OTHER RESOURCES

Download the podcast transcript

Go to the companion newsletter

NEWSLETTER ARCHIVE | SHARE WITH A COLLEAGUE

PROGRAM DIRECTORS

Mark S. Sulkowski, MD
Professor of Medicine
Medical Director, Viral Hepatitis Center
Divisions of Infectious Diseases and Gastroenterology/Hepatology
Johns Hopkins University School of Medicine
Baltimore, Maryland

Raymond T. Chung, MD
Director of Hepatology and Liver Center
Vice Chief, Gastroenterology
Kevin and Polly Maroni Research Scholar
Massachusetts General Hospital
Harvard Medical School
Boston, Massachusetts

Taryn Haselhuhn, BA, BSN, MSN, CRNP
Nurse Practitioner
The Johns Hopkins Hospital
Baltimore, Maryland

Podcast Transcript

BOB BUSKER: Welcome to this *e*ViralHepatitis Review podcast.

I'm Bob Busker, managing editor of the program. Our guest today is Dr. David Wyles, Chief of the Division of Infectious Diseases at Denver Health Medical Center and the University of Colorado. And our topic — a follow-up to Dr. Wyles's *e*ViralHepatitis Review newsletter issue — is Managing DAA Failures with the Newly Approved Treatment Options.

***e*ViralHepatitis Review is jointly presented by the Johns Hopkins University School of Medicine and the Institute for Johns Hopkins Nursing. This program is supported by educational grants from Gilead Sciences Inc., Merck & Co., and AbbVie, Inc.**

Learning objectives for this audio program include:

- **Explain the risk of resistance development following unsuccessful HCV therapy with direct acting antivirals.**
- **Discuss the impact DAA resistance and other negative predictors (for example, cirrhosis) may have on newly the approved retreatment options.**
- **Describe effective retreatment strategies for patients who have previously failed HCV DAA therapy.**

Dr. Wyles has disclosed that he has served as a consultant and/or advisor to AbbVie, Inc., Gilead Sciences, Inc., and Merck & Co., Inc. He has also received grant and/or research funding from AbbVie, Gilead Sciences, and Merck & Co. In his discussion today, Dr. Wyles has indicated that he will make reference to the unlabeled use of ribavirin with the sofosbuvir/velpatasvir/voxilaprevir combination, although such use is recommended in the current HCV treatment guidelines.

MR. BUSKER: Dr. Wyles, thank you for joining us today.

DR. WYLES: Thanks very much, Bob. I'm looking forward to our discussion.

MR. BUSKER: In your newsletter issue, you reviewed some of the newest information about successfully retreating patients who have previously failed direct-acting antiviral regimens. Our focus today is in translating those findings about the newly approved regimens into clinical practice. So please start us out with a patient scenario.

DR. WYLES: Our first case today is a 58-year-old white gentleman who comes back to the office to decide on next steps to treat his hepatitis C. He has genotype 1a and was treated in 2009 with pegylated interferon and ribavirin. He was treated a second time in 2015 with sofosbuvir plus ledipasvir with ribavirin for 12 weeks.

He had had a FibroScan assessment prior to that, which suggested he had cirrhosis. He tolerated his therapy well and had a viral load that was less than 15 copies at week 4 of therapy, but then relapsed after sofosbuvir/ledipasvir.

He has other medical problems including hypertension, hypercholesterolemia, and reflux disease. He's on medications to control those, including atorvastatin 40 mg and omeprazole 20 mg twice a day.

He has a history of remote alcohol use but stopped drinking in 2015. His exam is unremarkable, aside from findings in an obese male with a BMI of 37, but he does not have any stigmata of end stage liver disease on exam.

Routine laboratories include an albumin of 3.8, a normal INR, a normal bilirubin. His ALT is 57, his AST is 62, and his platelet count is 135,000. His creatinine is mildly elevated at 1.3. He had had imaging in 2015 with an ultrasound, which did not show any masses. He had no further imaging after that, and he is interested in retreatment.

MR. BUSKER: With this patient would you consider retreatment? And if so, what are some of the key factors you'd need to look at?

DR. WYLES: Yes, I would definitely consider retreating this patient, but several things need to be examined prior to starting his retreatment. I'd like to break those down into several classes or considerations.

One is the patient, himself. What are some of his characteristics that maybe made him fail his prior therapy and might impact

our choices on his next round of therapy? This patient, in particular, has cirrhosis. It appears to be compensated cirrhosis by the laboratories and other findings we're given. He also has mild renal disease with a creatinine of 1.3, which may impact our treatment choices.

His other factors include a history of alcohol use, although it sounds like this has been in remission since 2015; and he has a high BMI of 37, which may also work into our treatment responses with next rounds of therapy.

Of the other considerations related to his prior therapy, the most important thing to recognize is that this patient has already been treated with direct acting antivirals and to recognize the drug classes that he's been exposed to previously. In this case, the patient's been exposed to sofosbuvir and ledipasvir. Sofosbuvir is a NS5B nucleotide inhibitor and ledipasvir is an NS5A inhibitor, and those, as we'll discuss later, impact the possibilities of him having resistance and may impact future therapies.

MR. BUSKER: What role do you feel resistance might play as you consider his retreatment options?

DR. WYLES: Resistance to DAA therapies has been an interesting topic over the last several years and has undergone quite an evolution. Some of the articles we reviewed in this newsletter highlight the risk of resistance after failing a DAA-based therapy, particularly an NS5A inhibitor-based therapy. This patient had been exposed to ledipasvir in the form of sofosbuvir plus ledipasvir and took it for 12 weeks.

According to one of the articles we reviewed, he is very likely to have NS5A resistance. If you sequence his virus, probably about 95% of the time you would find resistance in a patient like this. Can resistance impact future therapies? It depends largely on the type of therapy we're considering.

First, within NS5A inhibitors there is a lot of cross-resistance. In other words, this patient has presumably developed NS5A resistance to ledipasvir. Most common mutations causing resistance to ledipasvir do tend to impact many of the other NS5A inhibitors available for retreatment, so there is a large degree of cross-resistance, particularly with resistance mutations at position Y93.

Prior to the new regimens we're going to discuss later in this podcast, there was evidence that resistance did impact future therapies. Patients who had resistance did not respond as well to a retreatment regimen. Specifically, one study looked at retreatment of a patient like this who failed sofosbuvir plus ledipasvir and used that same regimen again for 24 weeks. The study found that if patients had NS5A resistance going into that retreatment, only 60% of the patients with resistance going into that retreatment were cured when the same regimen was used for 24 weeks without ribavirin. The patients in that study did not have resistance going into that retreatment; everybody was cured with retreatment approaches.

So that's just one study that highlighted the potential impact of resistance on retreatments to these types of therapies.

MR. BUSKER: Are there other factors with this patient that need to be addressed prior to retreating?

DR. WYLES: Yes. As we mentioned, this patient has cirrhosis. An important component of managing a patient with cirrhosis is making sure we do other medical tests necessary to properly manage him. First is hepatocellular carcinoma screening. That's something that should not be forgotten. This patient last had his ultrasound in 2015. Current guidelines suggest an ultrasound or some other imaging modality every six months to screen for hepatocellular carcinoma, so before I treated him I would certainly make sure his imaging was up to date by getting another dedicated ultrasound to make sure there are no masses or evidence of hepatocellular carcinoma.

Next, since this patient is cirrhotic, another thing that needs to be evaluated is the presence of esophageal varices. In the history we didn't get an indication that he had had an EGD, so I would refer him to gastroenterology to have an EGD to screen for esophageal varices.

Finally, on that same note, in any patient with cirrhosis who is being evaluated for hepatitis C treatment — or retreatment in this case — I think we need to take at least a moment to pause and think about whether this patient needs to be referred to a specialist, say a hepatologist, for other evaluations of his liver disease; is this patient potentially a transplant candidate; and so on that should always be considered as you're thinking about treating a cirrhotic patient for hepatitis C.

MR. BUSKER: For your actual choice of retreatment agents, would you consider one of the newly available regimens?

DR. WYLES: Yes, I would definitely consider using one of the newly approved hepatitis C treatment regimens. We've had two new regimens approved in the last several months. Both these regimens, one unique aspect of them is that they have increased efficacy in patients who are hepatitis C treatment-experienced, particularly, patients who have been exposed to other hepatitis C direct acting antivirals and may have viral resistance.

The two regimens we'll discuss, one is a regimen called sofosbuvir plus velpatasvir along with voxilaprevir. This is a three-drug combination, essentially takes a prior regimen we've had, sofosbuvir-velpatasvir, and adds in a third drug, voxilaprevir, which is an NS3 protease inhibitor. It has advantages over prior protease inhibitors in that it's truly pangenotypic, meaning it

has activity against all the hepatitis C viral genotypes that is essentially the same in vitro. It doesn't seem to have any loss of activity against different genotypes, and it has a better resistance profile than many prior NSG protease inhibitors.

Now when we're looking at a regimen that has three different mechanisms of action all in one regimen, you get a regimen that is very potent against all genotypes and also has a very high barrier to resistance and has efficacy in patients with resistance who have previously treated.

Specifically, the major study addressing this population was the POLARIS-1 and 4 studies. We'll focus mostly on POLARIS-1, which evaluated this regimen for 12 weeks without ribavirin in patients who had been previously treated with a direct acting antiviral regimen including an NS5A inhibitor.

I'll just highlight the specifics of that study that pertained to our genotype 1a patient. Within that study in patients with genotype 1a, 96% of these patients were cured after 12 weeks without ribavirin. In fact, only one patient had viral relapse and one patient had breakthrough on therapy of over 101 patients t with genotype 1a who were treated.

This was the first large study that looked at a large number of patients with genotype 1a who had failed previously and showed excellent response rates.

The other major regimen that was just approved is a dual-combination regimen. It's a combination of a protease inhibitor, glecaprevir, with a new NS5A inhibitor, pibrentasvir. This regimen has only two mechanisms of action; both of these drugs again are pangenotypic and have high barriers to resistance, so together they form a very potent combination.

This regimen has not been studied as extensively in patients who are direct acting antiviral-experienced. The MAGELLAN-1 study, particularly the second part of that study, addressed a patient like we're discussing now, genotype 1a patients treated with NS5A inhibitors in the past, and showed with 16 weeks of treatment with that regimen a very nice response rate of 94% SVR.

One of the limitations and differentiations between these two regimens, however, is that the data backing the glecaprevir-pibrentasvir regimen in treatment-experienced patients is more limited. Specifically, when I mentioned 16 weeks of treatment with that regimen, only 18 patients were in that arm. That means we're talking about a much smaller number of patients, so our confidence in the data might not be quite as high.

Some other differentiators include drug interaction potential. For our patients, say, with atorvastatin, I would not recommend using glecaprevir-pibrentasvir in this patient; however, our patient was also on a proton pump inhibitor, omeprazole 20 mg twice a day, and that dosage of a proton pump inhibitor would not be recommended with a sof-vel-vox regimen. So there are some drug interactions to work around in this patient for both of these regimens.

Finally, our patient has compensated cirrhosis, but you don't want to forget those with decompensated cirrhosis. If you ran into decompensated cirrhosis, neither of these regimens would be recommended because they contain a protease inhibitor, which is not recommended in patients with decompensated cirrhosis.

To summarize, I think either of these new regimens is an option for our patient, working around some drug interactions. The data surrounding glecaprevir-pibrentasvir is probably not quite as robust, not as large a patient population, and the numbers with sof-vel-vox in genotype 1a NS5A-experienced patients, including those with cirrhosis, are excellent with a very high SVR rate, and only needing to use 12 weeks of therapy as opposed to 16 weeks with glecaprevir-pibrentasvir.

I'll remind our listeners that both of these regimens, the POLARIS-1 and the MAGELLAN study, were reviewed in our newsletter.

MR. BUSKER: Thank you for that case and discussion. And we'll return with Dr. David Wyles from the University of Colorado in just a moment.

MR. BOB BUSKER
This is Bob Busker, managing editor of *e*ViralHepatitis Review.

***e*ViralHepatitis Review is a combination newsletter and podcast program delivered via email to subscribers. Newsletters are published every other month. Each issue reviews the current literature in areas of importance to hepatologists, infectious disease specialists, primary care physicians, nurses, nurse practitioners, and other clinicians caring for patients with viral hepatitis.**

In the month following each newsletter, a case-based podcast discussion, like the one you're listening to now, is available to help translate that new clinical information into practice. These podcasts are also available as downloadable transcripts.

Subscription to *e*ViralHepatitis Review is provided without charge or prerequisite.

Continuing education credit for each newsletter and each podcast is provided by the Johns Hopkins University School of Medicine and the Institute for Johns Hopkins Nursing. For more information on this educational activity, to subscribe and receive *e*ViralHepatitis Review without charge, and to access back issues, please go to our website: www.eviralhepatitisreview.org.

Thank you.

MR. BUSKER: Welcome back to our *e*ViralHepatitis Review podcast. We're speaking with Dr. David Wyles from Denver Health Medical Center and the University of Colorado. We've been discussing retreatment of patients who've failed prior HCV DAA regimens. Dr. Wyles, please bring us another patient scenario.

DR. WYLES: Our next case is a 57-year-old Hispanic female referred for retreatment of genotype 3 hepatitis C. She had previously been treated with sofosbuvir plus ribavirin for 24 weeks. She took the entire course of treatment but did not follow up with that physician during her therapy. She had repeat hepatitis C RNA done about five months after completing that therapy and was redetectable with a viral load of 4.2 million. She was then retreated a second time with sofosbuvir plus daclatasvir for 12 weeks.

She has comorbidities of diabetes and obesity, as well as a history of bipolar disorder. She's on several medications including metformin, gabapentin, and aripiprazole. Her exam is benign, she does not have any stigmata of end stage liver disease. You perform a FibroScan in your office to determine her fibrosis stage and do basic laboratory studies. Her FibroScan shows suggestions of advanced fibrosis, possibly cirrhosis. Her laboratory studies are normal, including an albumin of 3.9, a platelet count of 154,000, and a creatinine of 0.7. An ultrasound shows borderline splenomegaly and increased liver echo texture consistent with chronic liver disease and possible fatty infiltration.

MR. BUSKER: This is a complicated patient. But before we get into that, she's HCV genotype 3. Talk to us about genotype 3 and give us some general background on why it's different.

DR. WYLES: Genotype 3 has been singled out with the advent of direct acting antivirals and has become recognized as a more difficult genotype to treat. But we shouldn't forget that genotype 3 has also been associated with accelerated liver disease progression and has increased rates of development of decompensated liver disease, as well as hepatocellular carcinoma when compared to nongenotype 3 infection.

Additionally, the epidemiology of genotype 3 is relatively prevalent globally, while genotype 1 makes up about 45% of infections globally, genotype 3 comes in second, but about a quarter of infections across the globe. It may also be increasing in prevalence in the United States as we're seeing more hepatitis C infections as a result of injection drug use.

The patient you described: based on her FibroScan and her labs, how would you characterize her fibrosis stage?

DR. WYLES: This patient is right on the border, so her FibroScan indicates advanced fibrosis, but the cutoff is very close to cutoffs typically used for cirrhosis. Additionally, while her labs are overall normal or consistent with chronic hepatitis C, her platelet count is mildly decreased and the ultrasound suggested borderline splenomegaly.

All in all, we have to realize the limitations of our noninvasive tests for staging. My approach would be to take a conservative approach in this patient, particularly since she's treatment-experienced. As I'm considering my retreatment approaches, I would consider this patient to have cirrhosis as I am thinking about my retreatment regimens and how I am going to implement them.

MR. BUSKER: Where does that assessment lead? How does it impact her retreatment options?

DR. WYLES: Historically, genotype 3 patients with cirrhosis, particularly those who are treatment-experienced, had among the lowest response rates to some of our other approved regimens for treatment of genotype 3.

It also seemed to have made some impact in the POLARIS-1 retreatment study. In that study, there were 78 genotype 3 patients and among those genotype 3 patients, the lowest response rate with 12 weeks of sof-vel-vox was seen in the subset of genotype 3 patients with cirrhosis. In that group, the sustained virologic response rate was 93%. That's still a very promising response rate but slightly lower than those without cirrhosis, where there were no virologic failures in genotype 3 patients without cirrhosis.

The presence of cirrhosis obviously also impacts our future medical care of this patient. We need to not forget about hepatocellular carcinoma screening and screening for varices, as we mentioned in the first case. Additionally, with the patient's high BMI and a possibility of additional liver insults such as fatty liver disease, things going forward for her medical care such as emphasis on diet, exercise, and weight loss, are things that should be considered.

There may be ways to modify therapy based on the presence of cirrhosis that we'll touch on later, to try to increase this, although these are not necessarily mentioned in the label recommendations for the use of sof-vel-vox.

MR. BUSKER: All in all, how would you approach retreatment in this patient?

DR. WYLES: First I would emphasize with the patient the necessity for adherence. She's gone through two different treatment regimens. Particularly with her first regimen it sounded like she didn't have much follow-up, so I would start with emphasizing adherence, that she needs to take her medication every day and that any missed doses could impact the response.

The next point, we've mentioned glecaprevir-pibrentasvir before, but it's important to recommend while that regimen can be used to treat genotype 3 infections, it has not been studied in NS5A-experienced genotype 3 patients, so that eliminates that regimen from a retreatment option for this patient.

I would go to sof-vel-vox to retreat this patient. As we discussed, with 12 weeks of therapy in genotype 3 cirrhotic patients, there was a relatively lower SVR rate of 93%. One potential approach would be to use sof-vel-vox for 12 weeks; however, in a genotype 3 patient who is NS5A-experienced and also has cirrhosis — or we're treating as having cirrhosis — I would add in ribavirin to this regimen, doing something like weight-based ribavirin plus sof-vel-vox for 12 weeks.

Now this is not mentioned in the label for sof-vel-vox, but the recent update of the hepatitis C treatment guidelines do endorse this approach, as well, for a genotype 3 treatment-experienced patient with NS5A inhibitor exposure and cirrhosis, to add ribavirin to that treatment regimen for 12 weeks.

MR. BUSKER: Thank you for that case and discussion, Dr, Wyles. We've got time for one more patient scenario.

DR. WYLES: Our last case is a 48-year-old African American gentleman. He also has genotype 1a hepatitis C. Comorbidities include hypertension, diabetes, and stage 3 chronic kidney disease. His exam is unremarkable. He had some noninvasive assessments of his fibrosis stage and was judged to be noncirrhotic based on a FIB-4 index, which was 1.19. He also had an abdominal ultrasound that was unremarkable. Of note, he did not have a FibroScan or a liver biopsy.

He was treated in 2016 with elbasvir-grazoprevir for 12 weeks. Prior to treatment he had baseline resistance testing, which did not reveal any NS5A resistance substitutions. He was treated but missed his SVR-12 appointment and came back about six months after completing therapy. At that time he now had a detectable hepatitis C RNA at 975,000.

On exam, he's an African American gentleman in no acute distress. His weight is 218 pounds. The rest of his exam was unremarkable. Again, no stigmata of end stage liver disease. Labs are notable for an albumin of 4.1, a total bilirubin of 0.6, an ALT of 79, and a platelet count of 256,000. His creatinine is 3.3, which gives him an estimated creatinine clearance around 38.

MR. BUSKER: You said this patient had previous baseline resistance testing. Tell us a little more about that and why it was done prior to his initial therapy.

DR. WYLES: Baseline RAS testing is recommended for certain specific populations when you're considering specific direct acting antiviral therapy. The only recommendation in a label for baseline resistance testing is with elbasvir-grazoprevir, which is the regimen this patient received; and in genotype 1a patients, which is this patient's genotype.

So the resistance testing at baseline was appropriate in this patient. That recommendation for resistance testing is based on some analyses which indicated patients with baseline resistance who had genotype 1a had a significantly lower response rate with elbasvir-grazoprevir if given for only 12 weeks. So in genotype 1a patients, the recommendation is to do baseline resistance testing when this regimen is going to be used.

In patients with baseline NS5A resistance, either this regimen is used then for 16 weeks with ribavirin, or another regimen should be selected. There is an impact of baseline resistance with some of the other direct acting antiviral regimens, particularly large reviews of phase 2 and phase 3 data with sofosbuvir-ledipasvir do show an impact of baseline resistance; again, predominantly in genotype 1a patients, particularly the subset of genotype 1a patients who are treatment-experienced. That impact is statistically significant in large analyses, and in treatment-experienced genotype 1a patients, it has been shown to be associated with a decrement in responses of about 15% to 20%.

The other place where there may be some impact of baseline resistance is in genotype 3 when looking at regimens such as sofosbuvir-daclatasvir or sofosbuvir- velpatasvir. In genotype 3 we're particularly considering the Y93H RAS. If that is present, it was seen with slightly low response rates, say, with sofosbuvir-velpatasvir in genotype 3 patients with that baseline resistance. There is no label indication to do baseline resistance testing with those, but some of the guidelines recommend considering doing baseline resistance testing in either treatment-experienced genotype 3 patients without cirrhosis or treatment naive patients with cirrhosis in genotype 3 prior to using sofosbuvir-velpatasvir.

MR. BUSKER: Would there be any reason to repeat the RAS testing now in this patient? What would you expect to find if that repeat testing was done?

DR. WYLES: In light of the approval of these new regimens, particularly for this patient and sof-vel-vox, there is no indication that resistance or doing baseline resistance testing is going to have any impact on responses or change the way you would treat this patient. Prior to the approval of these new regimens, it would have been reasonable to do resistance testing; in fact, most guidelines would have recommended resistance testing.

For this patient, since he was treated with elbasvir-grazoprevir, we would expect him to have baseline resistance. One of the articles reviewed in this newsletter looked at patients who had failed the elbasvir-grazoprevir regimen and the proportion that had resistance. Similar to sof-ledipasvir, nearly all patients who fail will have NS5A resistance. This regimen also includes an NS3 protease inhibitor, and again, the majority of patients failing have resistance to NS3 protease inhibitors. In this case, grazoprevir resistance is most typically in the form of mutations at position B168. However, in this study there is a difference, and during long-term follow-up, where NS5A resistance mutations remain detectable on sequencing out to two to three years, whereas NS3 protease inhibitor resistance mutations seem to be lost relatively quickly. So there is that differentiation between NS3 protease inhibitor resistance and NS5A resistance.

But ultimately in the clinical management of this patient I would not repeat resistance testing, because when we're looking at retreatment options, I would be considering sof-vel-vox. The data do not indicate an impact of baseline resistance on responses with that regimen.

MR. BUSKER: As you described this patient, he has stage 3 chronic kidney disease. What concerns would you have about how his CKD might impact his retreatment options?

DR. WYLES: Chronic kidney disease certainly can impact retreatment options. For this patient, with CKD stage 3 and an estimated creatinine clearance around 38 to 40, we're probably still okay but it needs to be monitored. I think it's important to note that chronic kidney disease is associated with chronic hepatitis C infection and there is some data to indicate that treating hepatitis C can prevent worsening of chronic kidney disease. This patient has multiple risk factors for his chronic kidney disease, so it's a little difficult to sort out. He's African American. He has hypertension and diabetes as well as hep C, so he has multiple reasons to be at risk for developing chronic kidney disease such as he has.

When considering retreatment, the main impact of chronic kidney disease is in those with an estimated creatinine clearance less than 30. It's at that point that labels and studies would have excluded patients from using sofosbuvir in their treatment regimen. And again, the regimen we'd be considering for this patient is sof-vel-vox. The concern with sofosbuvir surrounds its metabolite, which accumulates in patients with end stage renal disease, so again, a creatinine clearance less than 30. That does not directly impact our patient right now, but he is relatively close and it's something that needs to be monitored as he goes through therapy. But we can probably use it in this patient because his creatinine clearance is not below 30.

MR. BUSKER: What is your specific treatment option for this patient?

DR. WYLES: Glecaprevir-pibrentasvir, as we've discussed previously and reviewed in this newsletter, has only two mechanisms of action, an NS3 protease inhibitor, glecaprevir, with an NS5A inhibitor, pibrentasvir. And in the MAGELLAN study that looked at retreatment of DAA-exposed patients, this group of patients did not seem to do as well with retreatment using the same two mechanisms of action. Specifically, for our patient, since he was exposed previously to elbasvir-grazoprevir, a regimen which contains those same two mechanisms of action, reexposing him to glecaprevir-pibrentasvir was not associated with as high an SVR rate. Specifically, in the MAGELLAN study, the SVR rate was about 80% and it didn't seem to matter whether the duration was 12 or 16 weeks of glecaprevir-pibrentasvir.

So for this patient, I think that regimen is out. In fact, the label recommended such a patient is not to be retreated with glecaprevir-pibrentasvir. On the other hand, coming back to sof-vel-vox with three mechanisms of action, while you have an NS3 protease inhibitor and an NS5A inhibitor, you also have an added mechanism of action with the NS5B nucleotide inhibitor. In fact, patients in the POLARIS-1 study who were exposed to a protease inhibitor plus an NS5A inhibitor appeared to do just as well as those who were previously only exposed to an NS5A inhibitor without a protease inhibitor. For our patient, remembering his borderline creatinine clearance, sof-vel-vox for 12 weeks would be the preferred retreatment option.

MR. BUSKER: I want to thank you for bringing us today's cases and sharing your insights. I'd like to wrap things up by reviewing today's discussion in light of our learning objectives. To begin: the risk of resistance development following unsuccessful HCV therapy with direct acting antivirals.

DR. WYLES: The majority of patients failing a direct acting antiviral therapy have resistance. This is particularly the case for NS5A exposure following unsuccessful DAA therapy. In that case, looking at the various regimens which contain NS5A inhibitors, over 90% of patients are likely to have NS5A inhibitor resistance following that unsuccessful therapy.

Prior to the arrival of these new regimens — sof-vel-vox or glecaprevir-pibrentasvir — there was evidence that those resistance-associated variants selected would adversely impact future treatment regimens. However, with the advent of these new regimens, the impact of resistance on subsequent therapy has been mitigated substantially to the point that routine resistance testing after failing is probably not necessary as long as you can access one of these new regimens for your patients.

MR. BUSKER: And our second learning objective: the impact DAA resistance and other negative predictors (such as cirrhosis) may have on these newly approved retreatment options.

DR. WYLES: Resistance is now a limited predictor of responses; in fact, some detailed analyses of both of these new regimens, sof-vel-vox and glecaprevir-pibrentasvir, do not point to a prominent role of resistance in determining those responses, and resistance testing is not recommended before using either of these regimens.

However, some of the other key viral characteristics or patient characteristics are still pertinent. As we discussed in several of our cases, cirrhosis does have an impact on both the medical management of that patient going forward, as well as how the regimens might be selected. The addition of ribavirin might still be considered in a cirrhotic patient with genotype 3 infection who has failed an NS5A inhibitor before. Decompensated cirrhosis is certainly going to impact responses, because in that case protease inhibitors really should not be routinely used, and then the treatment options are much more limited.

MR. BUSKER: Finally: retreatment strategies for patients who have previously failed HCV DAA therapy.

DR. WYLES: To put together everything we've talked about in coming to a retreatment option for patients who have failed direct acting antivirals, there are a couple of key things to know. When you're considering glecaprevir-pibrentasvir, the patient's treatment history is key, and you have to know if they were exposed to an NS5A inhibitor, an NS3 inhibitor, or both. You must remember that if they've been exposed to both classes of DAAs in the past, even if not in the same treatment regimen, the recommendation would be not to use glecaprevir-pibrentasvir in retreating those patients.

The other important thing to remember about glecaprevir-pibrentasvir is that in NS5A-experienced patients who have genotype 1, the treatment regimen should be extended to 16 weeks. Finally, DAA-exposed patients with genotype 3, particularly NS5A inhibitor genotype 3, were not studied and are not recommended to be retreated with glecaprevir-pibrentasvir.

For sof-vel-vox, it's 12 weeks of therapy in any genotype patient who's been exposed to an NS5A inhibitor previously, and that includes patients who were exposed both to an NS3 and an NS5A inhibitor previously. So there you have this dual-exposed patient who can be retreated with this regimen. I think the key factor to remember with sof-vel-vox is that there were slightly lower SVR rates in genotype 3 cirrhotic patients and, in fact, all the genotype 3 failures did have cirrhosis. And although it's an off-label recommendation, the guidelines have recommended using ribavirin in a genotype 3 NS5A inhibitor-experienced patient with cirrhosis when using sof-vel-vox, and I think the data suggest that that's probably the best option, particularly since these are patients with advanced liver disease who have been through multiple other treatments and really don't have a lot of other options if they happen to fail a repeated therapy.

Finally, just keep in mind renal disease and decompensated cirrhosis, as those will dictate changes in regimens or which regimens can and cannot be used as you formulate your retreatment approaches.

MR. BUSKER: Dr. David Wyles from Denver Health Medical Center and the University of Colorado, thank you for participating in this *e*ViralHepatitis Review podcast.

DR. WYLES: Thanks very much, Bob, it was my pleasure and I really enjoyed our discussion today.

MR. BUSKER: To receive CME credit for this activity, please take the post-test at www.eviralhepatitisreview.org/test.

This podcast is presented in conjunction with the *e*ViralHepatitis Review newsletter, a peer-reviewed literature review certified for CME/CE credit, emailed monthly to clinicians treating patients with viral hepatitis.

This activity has been developed for primary care physicians, gastroenterologists, infectious disease specialists, OB/GYNs, physician assistants, nurse practitioners and nurses, and other clinicians diagnosing or managing patients with viral hepatitis.

This activity has been planned and implemented in accordance with the accreditation requirements and policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint providership of the Johns Hopkins University School of Medicine and the Institute for Johns Hopkins Nursing. The Johns Hopkins University School of Medicine is accredited by the ACCME to provide continuing medical education for physicians.

The Johns Hopkins University School of Medicine designates this enduring material for a maximum of 0.5 *AMA PRA Category 1 credit.*™. Physicians should claim only the credit commensurate with the extent of their participation in this activity.

The Institute for Johns Hopkins Nursing is accredited as a provider of continuing nursing education by the American Nurses Credentialing Center's Commission on Accreditation.

For nurses, this 0.5 contact hour Educational Activity is provided by the Institute for Johns Hopkins Nursing. Each podcast carries a maximum of 0.5 contact hour.

This educational resource is provided without charge, but registration is required. To register to receive *e*ViralHepatitis Review via email, please go to our website: www.eviralahepatitisreview.org.

The opinions and recommendations expressed by faculty and other experts whose input is included in this program are their own. This enduring material is produced for educational purposes only.

Use of the names of the Johns Hopkins University School of Medicine and the Institute for Johns Hopkins Nursing implies review of educational format, design, and approach. Please review the complete prescribing information for specific drugs, combinations of drugs, or use of medical equipment, including indication, contraindications, warnings, and adverse effects, before administering therapy to patients.

***e*ViralHepatitis Review is supported by educational grants from Gilead Sciences, Inc., and Merck, & Co., Inc., and AbbVie, Inc.**

CME/CE INFORMATION

ACCREDITATION STATEMENT
Physicians
This activity has been planned and implemented in accordance with the accreditation requirements and policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint providership of the Johns Hopkins University School of Medicine and the Institute for Johns Hopkins Nursing. The Johns Hopkins University School of Medicine is accredited by the ACCME to provide continuing medical education for physicians.

CREDIT DESIGNATION STATEMENT
Physicians
Podcast: The Johns Hopkins University School of Medicine designates this enduring material for a maximum of 0.5 *AMA PRA Category 1 Credit*™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

POLICY ON SPEAKER AND PROVIDER DISCLOSURE
It is the policy of the Johns Hopkins University School of Medicine and the Institute for Johns Hopkins Nursing that the speaker and provider globally disclose conflicts of interest. The Johns Hopkins University School of Medicine OCME has established policies in place that will identify and resolve all conflicts of interest prior to this educational activity. Detailed disclosure will be made in the instructional materials.

INTERNET CME/CE POLICY

DISCLAIMER STATEMENT

STATEMENT OF RESPONSIBILITY

STATEMENT OF NEED

INTENDED AUDIENCE

CONFIDENTIALITY DISCLAIMER FOR CME ACTIVITY PARTICIPANTS

HARDWARE & SOFTWARE REQUIREMENTS

COMPLETE CME INFORMATION

This activity was developed in collaboration with DKBmed.