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# Act Fast: Understanding Flu Prevention and Treatment in At-Risk Populations

Announcer:
Welcome to CME on ReachMD. This activity, entitled “Act Fast: Understanding Flu Prevention and Treatment in At-Risk Populations” is provided by Prova Education.

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Dr. Donnelly:
This is CME on ReachMD. I'm Dr. Cassandra Donnelly, and today I'm talking with Dr. Charles Vega. We'll be discussing the management of symptomatic influenza, our antiviral treatment options, their mechanisms of action, and the when and how of postexposure influenza prophylaxis.

Dr. Vega, welcome to the show.

Dr. Vega:
It's great to be here. Thank you for the invitation, Dr. Donnelly.

Dr. Donnelly:
Dr. Vega, when discussing annual efforts to reduce the spread of influenza, at the very heart of that discussion, our efforts are to reduce viral load and viral shedding of influenza A and B viruses. When successful, how is that reflected in disease transmission, duration of disease, and symptomatology?

Dr. Vega:
That's a great question. And it’s always good to go back to the virology of these illnesses to truly understand them. And you know, with influenza, the viral load is related to oftentimes how sick patients are; it's a good correlation. And then viral shedding is related to how transmissible influenza is. And that's very important for households, particularly where I see a lot of patients where their households are all at high risk for complications of influenza.

The number one way we can reduce both viral load and transmission of influenza is vaccination. But on the other end, we also underutilize antiviral agents against influenza. And those can also reduce viral load and reduce the risk of transmission as well. So it’s really a 2-pronged approach. You know, vaccination is, I think, the most important, but for patients who we suspect have influenza, particularly those at risk for complication of influenza, we really want to treat them with anti-influenza drugs, for themselves and also their families.

Dr. Donnelly:
Thank you for that answer. I'm so glad that you linked in the vaccination with the viral load. Many people are thinking these days about COVID-19 and about vaccination. And so it’s always important whenever we can to be able to link the importance back to let our colleagues and our patients know how we feel about that.

My second question is that you know that when you look at the 4 CDC-preferred antiviral agents for the treatment of influenza – so

oseltamivir, zanamivir, peramivir, and baloxavir marboxil – what can you tell us about these agents and their various indications for the treatment of symptomatic influenza? Who can receive these antiviral drugs? And when and how can they be given? And what is the route of administration?

Dr. Vega:
Great, great question. And yeah, it's nice to have some different choices when it comes to using different anti-influenza drugs. And 3 of the drugs – oseltamivir, zanamivir, and peramivir – are neuraminidase inhibitors, and that's a class we know. They've been out now for over 20 years. They're effective, well tolerated, safe. Baloxavir marboxil is a relatively new kid on the block. It's been around for only a few years and it is also effective, well tolerated, and safe, but it has a different mechanism of action. It works much earlier in the viral replication cycle, which has some implications for that issue of viral load that we talked about earlier. It's also – they have different indications as to the right age where we can start these different agents.

The one I use a lot is oseltamivir, and that really can be used at any age. It's indicated by labeling down to 14 days, so you can use it during infancy; we can use it in 99-year-olds; it's the preferred agent for influenza during pregnancy. That's a drug we generally know really well.

Zanamivir is the inhaled form of the neuraminidase inhibitor. And that's indicated for individuals 7 years of age and older. And the main worry with that inhaled drug is we want to avoid it in patients with chronic respiratory illness like asthma or COPD.

Peramivir is not used by a lot of clinicians because it’s an intravenous form of neuraminidase inhibitor. It's really used inpatient and mostly for folks who can't take oral drugs.

You know, baloxavir right now has the indication for individuals 12 years of age and older and is a onetime dose, which separates it from the neuraminidase inhibitors. For example, oseltamivir and zanamivir have a 5-day dosing period. So that is one thing that really makes baloxavir special—one time and done.

And all of these agents have an indication that they should be used within 48 hours of the onset of influenza illness. But remember that we can break that 48-hour rule for individuals who are at high risk of complications of influenza, which is a pretty long list. It's the patients I see every day who have diabetes, who have heart failure, who are 65 or over. It's a long list of those folks who are at high risk for complications or have severe progressive illness.

Dr. Donnelly:
So important to identify those particular individuals at high risk, the ages of patients that we should be really focused on, and of course, comorbidities – pregnancy, infancy – and who can use these medications. So thank you for delineating that for our colleagues and of course for our patients in the end

Now let's take a look at a short video that will put some of these ideas into context for our audience.

Announcer:
There are 5 stages of the viral life cycle: viral entry; uncoating, viral replication, assembly and budding, and viral release.

The life cycle starts when the influenza virus enters the host through the respiratory tract. The main targets of the influenza virus are the columnar epithelial cells of the respiratory tract, where viral hemagglutinin is required for binding to the surface of the host cell.

As the virus passes through the cell membrane, the viral membrane fuses with the endosomal membrane, and the M2 ion channel facilitates the release of viral RNA into the nucleus for transcription and translation.

Once the viral RNA enters the nucleus, an influenza-specific polymerase acidic endonuclease cleaves a portion of the host’s genetic code and replaces it with the viral RNA. This process of viral replication typically occurs within hours, producing numerous protein-based structures called virions that are then transported preferentially to the apical plasma membrane and released through a process called budding.

In an effort to get ahead of the sometimes severe influenza symptoms, there are several medications that target different stages of the viral life cycle. Let’s rewind back to the Uncoating phase. M2 ion channel inhibitors, or adamantanes, block the viral life cycle during the uncoating stage. However, these medications are no longer recommended by the CDC due to high resistance.

Neuraminidase inhibitors, such as oseltamivir, on the other hand, target the last stage of the viral life cycle and prevent the replicated virus from spreading to nearby epithelial cells, while the antiviral medication baloxavir marboxil disrupts the viral life cycle during the viral replication stage by inhibiting the influenza-specific endonuclease that is required for viral replication.

Dr. Donnelly:

Dr. Vega, now that the video has shown us where baloxavir marboxil fits into the viral life cycle, can you discuss some of the clinical data for this agent?

Dr. Vega:
So in two trials called CAPSTONE-1 and CAPSTONE-2, those trials involve folks – adolescents and adults with influenza randomized to baloxavir marboxil, one dose, oseltamivir, the 5-day course of treatment that's typical, and matching placebo. And they were looking at efficacy and tolerability. And what they found that it was that in both trials, both active agents baloxavir and oseltamivir outperformed placebo. And across the board, when it comes to anti-influenza drugs and symptomatology, if you take an anti-influenza drug, you're going to get better on average by about a day. If you take it really soon, early in the course of illness, say within 24 hours, you're much more likely to get more benefit than that.

But I think it's worth noting that in CAPSTONE-2, that's the largest clinical trial that's ever been done looking exclusively at folks at high risk of complication. And this is a strong group of interest in terms of treating influenza because now we're not just thinking about improving symptoms, we're really thinking about preventing complications. And I think it's notable that in that study, also, oseltamivir and baloxavir were both associated not just with improvement of symptoms versus placebo, but also a lower risk of complications and a lower use of antibiotics overall. And so those are very important outcomes when we think about the potential sequelae of influenza.

And I also want to note one other study that compared baloxavir and oseltamivir, and is that called MiniSTONE. And in that trial, it took kids between 1 and 12 years of age, and it was really a safety-based trial. It wouldn't be ethical to have a placebo group in this group of children, first of all. But what was found was that both baloxavir and oseltamivir were safe and were similarly effective in kids.

And I think just a couple other notes. I think one thing that separates baloxavir and oseltamivir in these trials and in clinical practice, oseltamivir is associated with a higher risk of nausea and vomiting. So if that's an issue for your patients, maybe have diabetic gastroparesis, or maybe they're having nausea and vomiting as part of the syndrome of influenza, baloxavir might be a better choice.

I think it's also worth noting that in all of these trials, viral load was reduced faster with baloxavir versus oseltamivir, and that's probably because it has that earlier mechanism of action in terms of the viral replication cycle. And it'll be interesting to see if that has implications in terms of household transmission of influenza.

Dr. Donnelly:
And super important information in regards to treating our children, and certainly in regards to viral load and the viral shedding. So thank you for that.

For those just tuning in, you're listing to CME on ReachMD. I'm Dr. Cassandra Donnelly, and here with us today is Dr. Charles Vega. We're discussing the management of symptomatic influenza, our antiviral treatment options and their mechanism of action, and the when and how of postexposure influenza prophylaxis.

Question number 4, Dr. Vega, oseltamivir, zanamivir, and baloxavir marboxil are now all approved for use as a postexposure influenza prophylaxis treatment. Can you give us some insight into what that means? First, what is postexposure prophylaxis? And in whom should it be considered? How do these agents rightly impact our disease transmission, duration, and symptoms? And finally, how do we select an antiviral agent for the patient with the patient's family that's sitting right in front of us?

Dr. Vega:
Yeah, great questions. And something that even myself in my practice sometimes forget. I often leave it until the very end. When I have a patient with active influenza and I'm writing them for an antiviral agent and talking about what to watch for in terms of potential complications. And then right before I leave, I'm like, "Hey, who do you live with again?" Because for my practice, a lot of multigenerational families living in pretty cramped conditions. And so I may be treating a 24-year-old who's otherwise healthy, but they live with an 86-year-old grandmother who's got heart failure, diabetes, and dementia. And so therefore, prophylaxis, particularly for her, and the risk of complications for her can be really, you know, quite high, and therefore, prophylaxis works. We should be using it more often.

You know, who qualifies? I kind of describe a scenario of a good candidate for prophylaxis. So it's somebody who's at high risk of complications of influenza. And again, that list is pretty long; it's most of the patients I see every day. And they have to have exposure to someone with a virus, so within the past 48 hours. When I talked about treatment of active influenza a minute ago, you go ahead and treat those patients at high risk of complications if you suspect influenza or if you confirm it with a lab test. You go ahead and treat those individuals regardless of their history of vaccination. Because with prophylaxis – if they had vaccination or are otherwise healthy, they probably aren't going to benefit a lot from prophylaxis. But if they only got the vaccine within the past 2 weeks or, of course, if they're unvaccinated, go ahead and write for prophylaxis for those patients.

You mentioned that the agents that are approved for prophylaxis – baloxavir, oseltamivir, and zanamivir – remember, with zanamivir and oseltamivir, it's a 7-day course of treatment after exposure. With baloxavir, it's a onetime treatment again. So that's the advantage. It's convenient, one time and done.

And the prophylaxis really works. In meta-analyses and in the baloxavir clinical trial looking at prophylaxis, the drugs are over 80% effective in the household transmission of influenza. So they really do work. Side effects are low. And I think it's worth noting as well that even if it didn't work, by giving prophylaxis, the infection that a household member might get from an infected family member is going to be less if they're on prophylaxis. So they're still going to be at less risk of severe symptoms, less risk of complications such as pneumonia.

Dr. Donnelly:
Yes, thanks for that. That's very important, as we often are encountering patients and family members who wonder, well, you know, they wonder, "If I did nothing at all, what's going to happen to me?" And so thank you for bringing that point home. It's obviously super important, and our patients and our colleagues are thinking about this.

Well, this has certainly been a fascinating conversation, but before we wrap up, Dr. Vega, do you have one take-home message that you want to share with our audience?

Dr. Vega:
Well, we have had a tremendous stress and terrible tragedy across this country and across the world with the COVID-19 pandemic, and it's certainly raised everyone's awareness, you know, clinicians as well as the general public when it comes to viral illnesses. But don't forget about influenza. We were blessed last year to have a very mild flu season. I don't think we'll be able to repeat that, especially as we open up things more in the United States. And so, you know, right now I'm certainly planning on vaccination against influenza for all my patients. I am going to have to watch the epidemiology of both influenza and COVID-19 during the upcoming flu season. And for patients who present with symptoms, co-testing and treatment. Treatment for influenza should not be held back when influenza is circulating in your community. So I think it is important. We're going to test for COVID-19; we're going to be testing for influenza. Let's treat those patients who need care.

Dr. Donnelly:
Absolutely. Testing, treatment, vaccinations, all very important topics that we'll be talking about for some time now.

Well, unfortunately, that's all the time we have for today. So I want to thank our audience for listening in and thank you, Dr. Vega, for joining me and for sharing all of your valuable insight. It was great speaking with you today.

Dr. Vega:
Well, thank you Dr. Donnelly. It was a great conversation.

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