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ReachMD

www.reachmd.com

info@reachmd.com

(866) 423-7849

Cases in Influenza Management: Aggressive Treatment in Older Adults with Comorbidities

Dr. Russell: Although seasonal influenza can be intensely debilitating in most individuals, in high-risk populations such as older patients and those with certain comorbidities, it can contribute to increased morbidity and even mortality. Fortunately, with the addition of a recently approved endonuclease inhibitor to the stable of neuraminidase inhibitors, there's a growing opportunity to personalize care and improve outcomes for these high-risk patients.

This is CME on Reach MD, and I'm Dr. John Russell. I'm the Director of the Family Residency Program at Abington Memorial Hospital in Abington, Pennsylvania. Joining me today is Dr. Nicola Hanania, the Director of Airways Clinical Research Center at Baylor College of Medicine in Houston, Texas. Welcome to the program, Dr. Hanania.

Dr. Hanania: Yeah, so, Dr. Russell, I'm glad to talk to you over the phone, and I would like to actually discuss a case with you, especially that you're in primary care. I'm in pulmonary medicine, and I think

we always scratch our head when we see patients like this one. So, I saw a patient around Christmas time last year. Her name is Pamela, and she's a 62-year-old woman who is a former smoker but has severe COPD. In fact, her lung function runs around, FEV1, around 40%, and so it's a stage 3 by GOLD criteria. This is also quite symptomatic in a way that she can barely do much, and she has an MRC dyspnea scale of 3, and she reported three exacerbations of the preceding year requiring antibiotics and steroids. So, in essence, this lady has GOLD stage 3, but she also is grade D based on the latest GOLD staging, a very high-risk patient. She is already on an inhaled steroid, the long-acting beta-agonist, as well as a long-acting muscarinic agent, so she's on triple therapy for her COPD, and this patient actually came to me around Christmastime as I told you earlier. She was actually complaining of aches and pains and subjective fever, and she reported that she was exposed to her husband who had recently a viral infection, which she thinks may be a bad cold, and obviously we were concerned about flu, and we asked her about flu vaccination, and she actually said she had received her flu shot a couple of months earlier. So, I'm curious to know in your setting, given her history and change in symptoms with possible exposure to influenza, what concerns you the most? And where do you start if you see this type of patient in your clinic?

Dr. Russell: Yeah, this is a tough case because Pamela certainly is a sick lady on a good day, and she certainly meets the textbook definition of someone who we're really worried about for influenza. So, influenza, depending on the season, has anywhere from 12 to 79 deaths per year if we look over the last 8-10 years. So, certainly she is a high-risk person, and she is a high-risk person if she just has a viral infection that's not influenza or certainly if she has a bacterial infection. So, I would be really worried about Pamela given her worsening respiratory symptoms. So, if I was seeing her in the office, I'm not sure exactly what I would do, but she's someone who really sounds like she is on the cusp of needing to come into the hospital.

Dr. Hanania: So, be it that she is a high-risk patient, and obviously we looked at her oxygenation, and she appeared to be stable enough to be treated in the outpatient setting at that point, having taken in consideration the risk factors and in being the rapid test came back negative, but given this high-risk individual, what do you usually recommend if you can treat her as an outpatient? Would you empirically treat her with an antiviral medication?

Dr. Russell: So, looking at 2019, what do we have available? Well, we have three neuraminidase inhibitors, one being an injectable, so I wouldn't be using that in the office. We have zanamivir, which is an inhaled medicine that I would not use in someone in COPD. So, really my choices are going to be oseltamivir or baloxavir. Both are oral medications. The baloxavir is a single dose. The oseltamivir is going to be b.i.d. dosing for five days. The mechanism of action is a little bit different, and I think to simplify it, the endonuclease inhibitors at a cellular level impact the production of influenza virus. The

neuraminidase inhibitors impact the release of the influenza virus from the cells. So, if we're looking at overall these medicines, both of them make patients better about a day sooner. There certainly are some studies that higher risk people, in treating them very early, that maybe we see a little bit of a bigger impact, but overall we're probably making people better about a day sooner. So, I would pick, you know, one of those two medicines, and partly that's going to be patient preference, partly that might be related to insurance, etc., but I certainly want to get a patient treated on one of these medications. Now, the baloxavir decreases viral shedding by about two days sooner compared to the oseltamivir, so certainly we decrease viral load a lot quicker using the baloxavir.

Dr. Russell: For those just tuning in, you're listening to CME on ReachMD. I'm Dr. John Russell, and I'm speaking with Dr. Nick Hanania about what action steps you can take when you have a high clinical suspicion of flu in a high-risk patient. But for our patient, Pamela, it's more than just the treatment of her influenza, correct? She has severe COPD. So, Dr. Hanania, what are some of the other considerations I need to keep in mind for a patient like Pamela in treating her beyond her influenza?

Dr. Hanania: Well, I mean, some of the concerns you brought up initially that you would probably even admit her to hospital because you're concerned about her, and you have a point. You know, these patients don't do well. They already have compromised lung function. Their airways are inflamed. They're not only inflamed but narrowed. They are at very high risk of complications, particularly pneumonia. As we know, COPD, even without the flu on-board, patients with COPD are at risk of pneumonia. A worsening COPD or exacerbation of the disease is not uncommon, and so these are the two things I would be very careful, and, in fact, sometimes it's very hard to differentiate, and the chest x-ray may be needed to look at whether there is an infiltrate. You may want to consider antibiotics if the fever is very high or their sputum is colored now and they're coughing more. So, as you know, with COPD exacerbation, we're very liberal with giving antibiotics. The big sticking issue here is systemic steroids, you know, where the viral infections usually try to avoid systemic steroids if possible, but certainly if she has COPD exacerbation, she may need systemic steroids, but we have to be carefully monitoring her after that treatment, and as you correctly mentioned, if she is on the borderline, hypoxemia is an issue. We have to admit her to a hospital to monitor her. Unfortunately, we lose several patients every year with COPD who have complication of influenza, and usually pneumonia is what unfortunately kills them.

Dr. Russell: Now, Dr. Hanania, I also understand that you were recently involved in presenting an abstract at the 10th edition of the Options for the Control of Influenza that was hosted by the International Society for Influenza and Other Respiratory Diseases. The study looked at antiviral therapy on short and long-term outcomes with COPD and influenza infections. Can you tell me about this paper that you presented?

Dr. Hanania: Yes, I sure can, and thank you for bringing it up. I think it's an important work. It was observational study, so you always have to look at these data with a grain of salt, but it allowed us to look at a large cohort for two large commercial claims database, one of Medicare and the other one of a private database. We looked at patients with COPD based on their ICD-9 diagnosis. We also looked at the diagnosis of influenza, so these patients had history of influenza infection, but in a subsequent analysis, which is the one that we presented in this conference you mentioned, we actually matched patients who have been given an antiviral at the onset of influenza within two days versus those who were not given an antiviral medication within two days of the diagnosis of influenza, and we wanted to look at health care utilization, certainly COPD exacerbation, admission to hospital not only a month after or a week after but also up to one year. Because of the large, huge database we had, it permitted us to look at these data longitudinally in this retrospective cohort, and not surprisingly, the baseline data that we looked at, we found that having influenza is bad for these patients. It not only prolongs risk of another exacerbation but also hospital admission, but what we were interested to find is that those who received antiviral treatment within two days had actually less health care utilization even up to a year in follow-up, including COPD exacerbation and hospital admission, and it didn't matter whether they were young or older so long as they had COPD diagnosis. So, actually our conclusion was very simple, that patients who have COPD like our patient here, Pamela, and with influenza, they display poor outcome over one year after their influenza infection, but those who receive antiviral treatment, at least in our cohort, within two days, had a better outcome and decreased health care utilization even one year after the infection. So, I think we're excited about these data. It proves the point to be cognitive about this risk for our patients with COPD.

Dr. Hanania: So, Dr. Russell, permit me if I can ask now that we're coming towards the end of the day's discussion – I think it's important to mention – I heard that CDC has reported that there may be some delay in the selection of the influenza A H3N2 virus component and the vaccine. While it's too soon to know whether this vaccine will be delayed, does this change your approach to these high-risk patients, and if at all?

Dr. Russell: Yeah, so if we look at last year's flu season, we had an H1N1 that kind of marched along that was a good match with the vaccine that did pretty well. There was an H3N2 strain in the first half of the season that the vaccine had a pretty decent match to, but by the end of the season, a new strain of H3N2 emerged that was really not touched at all by the vaccine. So, the vaccine makers kind of late in the, and it was a very long flu season as well, late in the game, they decided to change the H3N2 in this particular season. So, I think there is a delay, but I don't think it's going to be a delay that's going to be more than kind of the end of September for people getting vaccines. So, maybe there's not as much vaccine available in August, but hopefully we're going to have plenty of vaccine. What it's still

going to say to me is I need to vaccinate all my patients as possible, but when we look at senior citizens in the United States, only two-third of the seniors actually choose to be vaccinated, and then when I vaccinate folks to remember that the vaccine even in a great year might only be about 40% effective in a patient like Pamela. So, someone getting the vaccine, which I'm always going to encourage, is not going to be that magic bullet that's going to prevent someone like Pamela from being real sick, maybe ending up in the hospital, and perhaps dying from an influenza complication of her baseline COPD. So, for this year's flu season, in a patient like Pamela that we don't yet know what the efficacy of the vaccine is going to be, I would vaccinate him or her as soon as possible, and I would have a very, very, very, very low threshold for starting some antiviral influenza medication if they became sick with what I clinically thought was influenza.

Dr. Hanania: Yeah, and rather a point that we always worry about is that, you know, giving the vaccine early, you know, in these older patients, in fact, the effect may wear off. So, sometimes booster doses may be needed, and so I agree with you that it's not the, you know, we've seen so many patients with COPD who get influenza, and they were vaccinated, but the vaccine didn't work, and so you have to think about alternatives as well. So, before we say goodbye, I wonder if you have any take-home messages for the people listening, and I'll give my take-home messages as well. You start first.

Dr. Russell: So, we have some new medications available for us for influenza. The new guidelines from 2018 says every patient, regardless of how long they've had influenza, who is hospitalized in an American hospital, should receive influenza treatment with an antiviral directed against influenza. High-risk patients, being in the hospital or out of the hospital, should be treated with influenza antiviral medications. Low-risk patients who are seen within two days can be offered treatment, less of a recommendation for that, but certainly our hospitalized patients or high-risk patients, we should be thinking about antivirals directed against influenza. What are your thoughts?

Dr. Hanania: I mean, I agree. I think you really brought a very important point. I think obviously the general population is always at risk of influenza, but we have to be careful with people at risk. In this case, in our case today, one of the very important risk factors is underlying respiratory disease, and we talked about COPD here where we certainly have the similar issues, maybe to a lesser extent, in asthmatics who also have significant airway disease and can get really sick with influenza. So, I think one of the take-home messages I would like to bring up is to keep those patients under your radar. If you are a clinician and you face patients who may have an underlying influenza infection, and certainly sometimes it's very hard to tease out between that and a regular common cold, but if you have a high index of suspicion, consider treatment early rather than late because many of these patients end up in the hospital, and some unfortunately may not make it if they have complications like pneumonia and respiratory failure.

Dr. Russell: And with those key takeaways in mind, I'd like to thank Dr. Nicola Hanania for joining me in this discussion. It was great speaking with you today, Nick.

Dr. Hanania: Great to speak to you. Thank you, Dr. Russell.

Dr. Hanania: It's a pleasure. Thank you for having me.