

## INFECTIOUS COMPLICATIONS

SANDRA E. KURTIN, RN, MS AOCN, ANP-C I'm delighted to have our next speaker join us. Please welcome Dr. James Lewis of the Oregon Health and Science University as he discusses Best Practices in the Management of Infectious Complications for Cancer Patients. Welcome.

DR. LEWIS: We're going to have a good time talking about infectious complications in cancer and we're going to spend some time specifically talking about these learning objectives right here. You are all advanced practitioners; therefore, I have extremely high levels of faith in your ability to read, and I am not going to read these lovely learning objectives to you.

Here are my disclosures; you can read those as well. Again, I have no questions about your reading skills.

Let's cut to the chase. How many of you have used biosimilar filgrastim at this point? Cool. That's about what I expected. Biosimilar filgrastim was the first of the biosimilars that we've seen come to the market in the United States. As we sit in this room today, we currently have four biosimilars that have been approved by the FDA at this point in time. It is anticipated that by 2020, this market has a potential to be up to a \$4 billion a year market just in the United States. And the reason for that is that the agents that we're talking about tend to be very expensive progenitor agents. And what we're noticing is that the biosimilars as they come along, because of the complexity of manufacturing and then some

other things that we're going to discuss, the price has come down somewhat, but they're not coming down huge at this point in time.

When you talk about biosimilars versus generics, one of the big questions I get is, "All right, aren't biosimilars generics?" There's nobody here from the FDA is there? Because I'll tell you right now it looks like, it barks like, it smells like, it's pretty much a generic, okay? But, unfortunately, what has happened is when we talk about generics as we're used to thinking about them, they're small molecules; they're easy to make; they're easy to verify and they're fairly straightforward. What you see with the biosimilars is that you have extremely large, extremely complicated molecules that are produced typically from living systems. They're proteins, they're massive, and so the complexity of the molecule is much different than anything that we've seen before as far as our standard generics go. But for a lot of the other intents and purposes, you should think of them as generics. You should think of them as really, really complicated generics is what this boils down to.

The other thing that I want to make abundantly clear as we move through and talk about the biosimilars for filgrastim here, is that you have to understand that unlike generics at this point in time, these are not easily interchangeable. You can't just flip back and forth at this point and time, and that's because of the pathway that was put together for the approval of biosimilars and how the wording works.

Let's be real here, if you accidentally switch up a dose of biosimilar filgrastim for the original filgrastim, are you going to hurt the patient? No. In all

likelihood, you are absolutely not going to hurt the patient because you still need to remember that these drugs to get to market have been through extensive screening through the FDA, and the FDA puts them through a ton of hoops. But because these molecules are so big, so complicated, and have some subtle structural differences and there's not a lot of experience with them at this point in time, the recommendation remains that they should not be interchangeable. Whatever agent starts a patient's regimen should ideally be what you stick with through the remainder of the therapy.

As we stand here and talk about biosimilars today, no, none, zip, zero, zilch of the four approved biosimilars are considered interchangeable by the FDA, all right? That's a very, very important point to make. And that's one of the major differences that we see between biosimilars and generics. When you look again at the structure of the molecules, on the right is a molecule that probably you're very familiar with: cefepime, our favorite fourth generation cephalosporin in febrile neutropenia. On the left is the chemical structure of filgrastim. Which one of those would you like to try and make, right?

I will you tell you that the cefepime molecule is way, way, way, way easier, and that's the challenge with the biosimilars. You can have the same amino acid sequences, but the proteins may be folded a little bit different or there may be something that's just a smidge different. But what you need to remember at the end of the day is that in order to be called a biosimilar, there's been extensive pharmacokinetic and pharmacodynamic work. The amino acid sequence is the same, these things are virtually identical, but there are subtle differences

because of the complexity of the molecules that are not felt to be clinically relevant. That's why there's still a little bit of hesitancy about switching back and forth and why we really want to stick with -- if you go with the biosimilar out of the gate stick with that through the remainder of the patient's therapy. If you start with the brand name, stick with that through the remainder of the patient's therapy.

This is looking at all of the various steps that go into producing large, complex protein products like we're used to seeing with biosimilars and all the other -mabs, -mibs, etc., that you all deal with and why are so much more complicated to deal with than the small molecular generics that we're used to dealing with.

What have we seen in the market with regards to filgrastim versus what that's done with filgrastim? You can see here some numbers that I pulled from Amgen's Quarterly Report as to what the impact of biosimilar filgrastim in the United States has been thus far. What you'll notice is that total sales are still on pace to basically do \$600 million in the U.S. -- not a bad number. But realize that's down somewhat substantially.

There's the two biosimilars that we've talked about there, although realize that tbo-filgrastim is not technically a biosimilar, it's something that was approved prior to the 2010 regulatory pathway for biosimilars and it only has the one indication. That bottom line on this slide is very telling, and this is why I think more of you didn't raise your hand. The challenge that we see with biosimilars is we're still trying to figure out the wording, we're still trying to figure out payer

structures and whatnot, but because of that and because of the fact that the acquisition cost for your pharmacy isn't that much cheaper, there hasn't been a huge run. Typically what we see with generics is you can see up to 50 to 75% increases in price within the first 12 to 18 months after a generic hits the market.

What we've seen with the biosimilars is that maybe it's a 10 to 20% decrease in price, so the financial incentive to move hasn't been quite as forceful as it might have been with a generic, plus some of the confusion about biosimilars. If you look out there when you say biosimilar to a lot of physicians and a lot of providers, they're still not sure what that means. We have a long way to go with education, and there are a variety of issues that have kept us from seeing rapid acceptance of the biosimilar filgrastim into the market.

That's a little bit of background on what biosimilars are, where we stand and what's going on from an economic standpoint. Let's talk a little bit about where we're going clinically with these things. What the guidelines have to say – and these are taken from the NCCN guidelines, the 2016 version, so they're readily available to you online. If you have not gone around and dug in the NCCN guidelines section on the web, I would strongly encourage you to do it. There is a broad scope in depth of guidelines available on that website and they're very concisely written. They're easily searchable because they're in PDF form and they work very, very nicely.

One of the things that the guidelines say with regards to biosimilars that I think is important is that you notice here that the G-CSF now refers to all of these approved agents. The guidelines have moved wholesale over to basically saying,

“When we say G-CSF, we’re talking about any of these products.” What you see right there is that the guidelines have already taken them up and accepted them. They say in here that biosimilars can be substituted for the originator product, but, again, it’s very important to realize that they go on and say, “If it’s been considered interchangeable by the FDA.”

Remember, none of the currently available biosimilars have been considered interchangeable at this point in time, so whatever regimen you start with is what your patients should complete therapy with; again, recommending that patients remain on the same product throughout treatment and, again, making the comment down here that it is not an interchangeable product for you.

What are some of the challenges that we face with some of these biosimilars and filgrastim as we move forward? It’s unlikely that we’re ever going to see phase III trials with these. Because all the FDA is requiring is head-to-head data showing that the product is equivalent to what you have out there. So going back and doing a full phase III trial would be really expensive and probably not terribly interesting to allow the manufacturers. Our data is then being extrapolated from some of the earlier head-to-head safety data to other indications. Guys, that’s fine. Don’t get hung up on that.

The number of hands that I saw go up in the room already, one of the things that I’ve heard is, “Oh, but, you know, we don’t have data in that indication.” Come on, come on, you have the same amino acid sequences; you have all kinds of PK/PD workup by the agency; you know these drugs are going to work. So I really, really don’t like a lot of these comments, although I

understand why we have to do it in an area where we're dealing with these new agents. Saying that we should be sitting around making decisions on appropriate and corporation -- the drug is way cheaper. How many of your patients enjoy getting bills that are 20% higher than they need to be? Again, I think that we should be encouraging rapid integration of these biosimilars into our product.

They basically say that the biosimilars have some variation in manufacturing. Again, remember that the standard of the FDA is holding these agents to account for a lot of what we're talking about here. You're talking about what the FDA by definition says is insignificant differences between the compounds; they're not felt to be clinically relevant at all. Should we pay attention to them since we've not used these molecules before? Absolutely we should. But it shouldn't be a situation where we're basically costing our institutions and our patients considerable money by not moving in these. And I don't necessarily agree that these could result in differences in efficacies because, again, you have to prove a lot of that to get the biosimilar tag.

The safety thing? A lot of safety signals don't pop up until way late in the game. We've seen this with antibiotics for years. Think about quinolones. Quinolones have a brand spanking new black box warning; ciprofloxacin has been on the market since 1986. When you start to get into safety signals you have to realize that a lot of times they happen very, very infrequently and it's going to be years before you see anything pop up from a safety signal. So I don't worry about efficacy at all with regards to the biosimilars.

And the safety? We can talk about that, but remember how structurally similar these molecules have to be? And we will see a lot of experience with these as we move forward because of the less expensive nature of the compounds.

The FDA-approved indications that you have for the biosimilar filgrastim are exactly the same as what you have for filgrastim -- no difference there whatever. Notice the tbo-filgrastim because it was approved prior to the biosimilar pathway only has one indication and that's reduction in the duration of severe neutropenia and nonmyeloid malignancies. Filgrastim indications are basically exactly the same as the biosimilar indications, which tells you what the FDA thinks of the similarities between these two molecules.

When you think about these clinically, who should we be giving these agents to? Who should be getting myeloid growth factors? The big thing that should drive this is the intensity of the chemo regimen. The harder you're going to smack them and the more marrow toxic that these agents are, the deeper the neutropenia is likely to become, the more likely you are to need to be using these agents in prophylaxis-type settings. Any chemo regimen or any patient who is felt to have a higher than 20% risk of febrile neutropenia is recommended to receive myeloid growth factors as prophylaxis; again, the type of chemo regimen and other risk factors.

When you start talking about other risk factors, what I want to draw your attention to is right down here. Once again we know that getting old is dangerous. Find me any disease state where when studied, getting older results

in a better outcome. I cannot think of one. I'm sure someone in this brilliant room will, but I can't come up with one. If you have an older patient who's receiving big-time chemo and then they've had previous chemo or radiotherapy, pre-existing neutropenia or a tumor involvement of the bone marrow, or poor performance status and a bunch of comorbidities.

So the more frail the patient becomes, the more they've been around the block, the more their marrow has been hit, the more you need to be thinking about these. Because we know that when these agents are used in the appropriate patients, they reduce infection rates, they reduce hospitalizations, they reduce length of stay; there's a lot of upside here.

The downside that you will hear repeatedly is spot-on correct; they are expensive. These are big cash money drugs, which is why the biosimilars have gotten so much attention. Because 20% less of a big number is a big number. And that's what is getting a lot of pharmacy directors' attentions and whatnot.

Thinking about which folks should be receiving these agents, this is what you're looking for right here, with the understanding that comorbidities, frailty, types of tumor, etc., also this. The other thing to notice is that all of your major oncology organizations agree here, and that's always nice when the smart people can agree on what to do. The intermediate risk folks, it's a little bit trickier, but I'll tell you right now if it's my mom or dad, I'm going with it because the data that's out there suggests that you decrease infection rates, you decrease length of stay, you decrease duration of neutropenia.

One of the pushbacks that you'll hear sometimes is, "Yeah, but there's no evidence of improved mortality." Guys, the bad news is these don't treat the malignancy. One of the problems with hanging up on mortality as an endpoint is that malignancy comes with a pretty high rate of mortality in and of itself, so I'm not sure that mortality is the best endpoint for us to be looking at with these compounds.

What about people who are sick and come in? What should we be doing with myeloid growth factors in patients who are infected? This is where the data starts to get dicey. Most people agree that prophylaxis use in high-risk patients makes a lot of sense and that the data is fairly substantial. The therapeutic use of myeloid growth factors in patients who are infected is a much more dicey area and an area where it's harder to find good data. So it's much less well-supported by the evidence, but what we seem to see in these studies is that it's associated with a shorter length of stay; it's also associated with a shorter duration of neutropenia.

However, you're not seeing necessarily a decrease in mortality. There is some suggestion of a decrease in infection-related mortality, which to my way of thinking is all you can ask these compounds to do. The other thing that I want to point out -- we bumped into this a couple times in our cancer patients up in Oregon -- if somebody is on pegfilgrastim -- remember that that's like an every 3-week dose -- if someone comes in infected and has received a dose of that, there is absolutely no benefit to doing anything with regards to giving them

further growth factor in order to try and improve neutropenia recovery. It's just not going to be a benefit at all, and all it's going to do is add cost to the patients.

When you think about patients who are presenting with active infections, one of the things or what the patients who I think that you should be considering myeloid growth factors in are in this list right here. Folks over the age of 65, if they are also -- and before I go any further, let me stop there. Notice here, "Did not receive myeloid growth factor prophylaxis." If they'd been receiving myeloid growth factor prophylaxis, continue it. If they got pegfilgrastim, don't hit them with another dose, but if they've not been seeing this at all and they come in septic, especially with an ANC of less than 100 or a neutropenia that's expected to last longer than 10 days, I think you can make a very good argument for myeloid growth factors in these patients.

If they have pneumonia, especially if they have invasive fungal infections or other kinds of tough to treat infections, those are the areas that I would encourage you to think long and hard about the use of these compounds. When you look at them for stem cell transplant, what they're primarily used for is mobilization of the peripheral stem cells and also are used somewhat after transplant. But realize that this is a controversial area and not all centers necessarily agree on this. They are recommended, though, routinely as supportive care post-transplant.

That whole discussion around filgrastim is because there are certainly situations where having white cells is a really, really good thing. This person back here sneezing clearly needs more white cells. See what happens when your

white cells leave you? You end up with a cold. Some of the reasons that I am a huge white cell fan are these guys right here. One of the things that we are seeing nationally and internationally is the emergence of a variety of bacterial pathogens that we've seen before, but now they're nastier.

If you go back 20 years and you come up to me and you say, "Jim, what's the rate of carbapenem resistance in *Klebsiella*?" I'd be like, "0." But do you realize that in New York City, depending on which hospital you're in, up to 40% of *Klebsiella* isolates are now carbapenem resistant. And for those of you who checked out of pharmacology a little bit early, bad move, bad move. Remember that the carbapenems are the Bazooka-mycins or the Godzilla-cillins of the antibacterial world. They are "kill 'em all-a-mycin" for lack of a better term.

When you're carbapenem resistant, you're resistant to all of your beta-lactams; your penicillins just died, your cephalosporins just died, your carbapenems just died, your aztreonams just died; doesn't leave you with much, does it? And therein lies our problem. I think one of the things that I'm increasingly becoming a growth factor fan for is that prevention of infection because infection leads to antibiotics, antibiotics lead to this. The only way that we have ever won in infectious disease is through vaccines. That's the only time that the bacteria or the viruses have ever gone, "Too good. You win. Peace out."

Did you guys see we just eradicated measles from the Americas? I almost said the Northern Hemisphere, but that's not right. We eradicated measles from the Americas until someone doesn't get vaccinated and goes to Europe and flies home. But vaccines work. The antibacterials, the bugs don't quit. While we're

sitting here, the bugs are listening to us talk and they're thinking about ways to get around the antibiotics that we are talking about. We say that bugs don't have brains; if any of you have ever looked at the mechanism behind vancomycin resistance in enterococcus, they have brains, we just haven't found them. Because those steps, it's way too complicated.

What we are seeing is a rapid emergence of organisms that are increasingly difficult to treat. Remember 80%, 8-0, of the antibiotics that you have available to manage your patients are beta-lactams. So when you start saying all the beta-lactams are dead, think about what that does to your therapeutic armamentarium right there. Resistance in these organisms is extremely challenging. This is a list that comes to us from the CDC and is some of the things that they are concerned about.

How many of you are just over C. diff? You're so sick of C. diff you can't even see straight, right? I am telling you right now, do you know C. diff. is right now the number one healthcare-associated infection in the United States, number one? No matter what we do, we do not seem to be able to get our C. diff rates down in Oregon. This is a huge challenge; it is definitely associated with excess mortality. Carbapenem-resistant Enterobacteriaceae; when you have E. coli and Klebsiella-resistant carbapenems, you know you're having a bad day. Unfortunately, your types of patients are the patients who show up with these organisms; they've had round after round of antibiotics because they're chronically ill, they're debilitated, they've seen chemotherapy. They have plastic in place, all of the things that set them up for recurrent infections; they have

tumors squeezing on organs that don't like to be squeezed on, things like that that result in problems.

Drug-resistant gonorrhea -- we can tell lots of jokes about that over break, but we're not going to be too concerned about that. But where you guys should be concerned: multi-resistant pseudomonas and Acinetobacter. Realize when we talk about febrile neutropenia that historically the bug that terrified us was pseudomonas aeruginosa. Pseudomonas aeruginosa; it's mean, it's green, and it eats everything is what you need to remember. The stuff can live in jet fuel.

What we see now is that we're seeing more and more pseudomonas strains emerging with resistance to a variety of antibacterials; ESBL-producing Enterobacteriaceae. E. coli, anywhere you go, is the number one Gram-negative organism, and so substantial resistance in E. coli is going to result in a lot of problems. Your quinolone prophylaxis that we use widely in some of our more profoundly compromised patients, have you noticed the E. coli's coming in when people are quinolone prophylaxis? They're always quinolone resistant, aren't they? You can hear them laughing at you, which is very insulting. But it's another reason that we need a vaccine.

When you think about antibiotic resistant bacteria, what the CDC estimates is that more than two million illnesses and at least 23,000 deaths are attributed to this in the United States every year. If we can get our infection control right and if we can do a better job of being antibiotic stewards, it's estimated that we could potentially have 70% fewer patients than estimated develop CRE infections in the next 5 years. The problem with CRE, carbapenem-

resistant Enterobacteriaceae, is that it's not just carbapenem resistant, it's pan-beta-lactam resistant; they're typically quinolone resistant, they're typically aminoglycoside resistant; they're basically nightmare bugs for lack of a better term. And they're very problematic in certain geographic locales and in certain hospitals.

But one of the things we need to be better at in healthcare in this area is we need to be better at integrating our systems. We can be absolutely awesome in our hospital, but if the hospital down the street doesn't wash their hands and sends us their patients, we're going to have all the same problems they have. Some great data that came out of Chicago -- when you move patients from Nursing Home A to Nursing Home B, back to the inpatient side to another hospital over to this nursing home, that patient's bugs go with them everywhere. We need better systems to allow us to track patients who are moving from institution to institution with resistant organisms. These are the types of challenges that we're talking about.

I have to tell you, I love coming to oncology meetings because you guys walk up to each other and you, "Blah, blah, blah -mab, blah, blah, blah -mib, blah, blah, blah -mab, blah, blah, blah -mib." And I'm, "What are these people saying?" It's like watching old *Mork and Mindy* reruns. Blah, blah, blah -mab, right?

In the time I've been standing up here talking, five new oncology agents have been approved by the FDA. As an ID person, I am bitter and angry. This is what I've gotten to deal with for the last 20 years. And now I will tell you that if you extend this out from 2013 to 2016, we've had six new agents approved by

the FDA. You guys are like, "Six? Pfft, we'll have six by the time this presentation's done." But for me, that's a big freaking deal because what we've noticed is that Big Pharma has gotten out of anti-infectives because, again, how many of you are involved with your P&T committees? Anybody? So there are a few of you.

I need to see you people after this meeting because you guys walk in, you're like, "We're going to use blah, blah, blah -mab." And the P&T committee says, "Well, how much is blah, blah, blah -mab?" And you guys are like, "Mm, we anticipate we'll take care of 20 patients with this this year and we'll spend \$2.3 million." And the P&T committee goes, "Clap, clap, clap."

I walk in, I have a new antibiotic, we haven't seen a new antibiotic in forever, and I'm like, "This antibiotic costs \$400," and they're like, "What? What?" And they're like throwing crap at me. I need you people to teach me how you Jedi mind trick the P&T committee because they're like, "\$2.5 million, clap, clap, clap." You guys kill me. And I love you, but I'm jealous as all get-out.

I want to back up here real quick. The problem is that we know that oncology's where all the money is and we can have some interesting debates about how long that's sustainable, but I figure that's a whole other session. One of the other issues, though, that makes antibacterials so not effective is, as I've already pointed out, the bugs don't stop. The bugs never stop. Our two newest Gram-negative agents, ceftolozane/tazobactam, ceftazidime/avibactam, within a year and a half of our lease, we've already got cases in the literature of pseudomonas figuring them out and other things figuring them out.

Have you ever, ever seen cholesterol that is resistant to atorvastatin? I bet none of you have driven by the donut shop and went, “Not eating there; that cholesterol donut, that’s resistant to atorvastatin.” The problem is that antibiotics are a limited finite resource, and you have crazy people such as myself running around trying to get you people to use less of them. If you’re in Big Pharma, where is the incentive to continue to develop these compounds? We have to re- envision how we’re incentivizing Big Pharma to stay in this game because you can’t have untreatable bugs roaming around on your units; it is absolutely no fun. And there are places in this country and places in this world where that is the case today.

We’ve already talked a little bit about some of these organisms that are causing most of the problem. Again, notice that *C. diff* is sitting at the top of the list, but look, the thing that’s really disturbing is these are all the usual suspects and they are still the most common causes of healthcare-associated infections. When these suspects become highly resistant and common, that is not a good place to be. When you look at carbapenem resistance in *pseudomonas*, because, remember, *pseudomonas* is what historically scares the bejesus out of us when it comes to febrile neutropenia. Notice that there are a lot of places in the country that are well in excess of 20% of their *pseudomonas* isolates being carbapenem resistant.

The other thing that we know is that when you have organisms that are more resistant, notice what it does to length of stay; notice what it does to hospital costs. Not only are these bugs harder to treat, they keep you in the

hospital longer, you cost more money, and unfortunately, you're more likely to die with these. Patients who are found to have infections with carbapenem-resistant enterobacteriaceae typically have a mortality rate of approaching 40%. That means four out of 10 of those patients leave the hospital through celestial discharge. Which is not the way we like our patients leaving the hospital.

The other point that I want to make is E. coli. This green bar and this green bar is E. coli. This is all the other bad Gram-negative kids that we talk about and worry about. When you look at your antibiogram and you see that your institution has a 20% rate of E. coli resistant to fluoroquinolones, it becomes a big deal because the number of isolates that you see of E. coli every year is so high. Any significant resistance in E. coli whatsoever is a significant clinical problem because of the frequency with which that bug causes infections.

You don't have to be horribly immunocompromised for E. coli to be problematic in you, but if you are immunosuppressed it enjoys you even more. When we think about who's at risk for these multi-resistant Gram-negative organisms, notice again that getting old is highly dangerous. Once more we see that getting older is dangerous, but exposure to broad spectrum antibiotics, increasing numbers of antibiotics, older age, chronic disease, ICU, COPD, increasing duration of hospitalization -- does this sound like any patients you guys see? Therein lies the problem, and that's why we need to be doing everything we possibly can to minimize antibiotic exposure in these patients and also to ensure that we get their white cells back in a timely fashion to try and minimize their infection risk.

This slide largely talks about what we've already touched on, that across the board, whether it's cost, whether it's length of stay, whether it's mortality, everything gets worse when you have multi-resistant Gram-negatives causing the problem.

The other thing that I want to remind you guys of is that when a patient appears septic in your ER or appears septic in your outpatient infusion center, realize that time is of the essence. This is one of the reasons that the CMS is focused on sepsis as one of the core measures is such a big deal because we know from this study and a couple of others. What I want you to notice here is the Y axis here, this is the percent of patients who survive. Notice within 0 to 0.5 hours, you've got about an 80% survival and then it goes down. This is the effect of the time of antibiotic initiation over here, so if you're out in here and it took you 36 hours to get effective antibiotics onboard and this patient was septic, their survival rate is 5%.

The way that this data rolls out is that for every hour of delay in effective antibiotic therapy in someone who is sepsis, you increase their mortality risk by 7%. So time is of the essence when patients are hemodynamically unstable, critically ill; you need to be making sure that you're choosing appropriate antibiotics and getting them onboard in a timely fashion.

The other issue, to wrap up this fun-filled discussion section, how many of you have used or seen colistin? Some of you. Colistin is basically intravenous Tide laundry detergent; it is thoroughly unpleasant. It was put on the shelves in the 1950s because it was -- wait for it -- more toxic than aminoglycosides.

Aminoglycosides cause your kidneys to fall out and lay on the floor. It was a crappy drug in 1955 and it's a crappy drug now, but, unfortunately, it was our last line for a lot of these resistant Gram-negatives until we started feeding it to pigs in China. So now what we have are organisms coming out of China that have spread globally that are colistin resistant.

Coming back to the point that we have to be not only careful about how we use antibiotics in our patients, but also how we use antibiotics as a society because we have burned it down to some of the last few options. You guys are now left in a clinical scenario, and I say "you guys" because I left the building as soon as I heard it was carbapenem resistant. You're dealing with a situation where you have increasing resistance rates and you have compromised patients who are at various risks of developing these infections. Your immune system is clearly your friend. We know that we need to get that back and we know that from long-term data that neutropenia drives your infections. And the longer your neutropenia persists the more likely you are to develop infection.

When you think about who is at high risk that you see in front of you, the first thing that predisposes through infection is immunodeficiency neutropenia but also when you see folks with mucositis, when you see folks who have impaired organ function because of tumor burden or because of radiation to certain areas, you really need to be thinking about that.

The other thing that we don't think about quite enough sometimes is my personal favorite, and that's the medications. As I've pointed out, you guys are all -- as we're sitting here -- you guys have had five new agents approved for

management of oncology and the problem with a lot of these -mabs and -mibs, we don't know the full extent of the side effect profile until they're out in the clinical practice for a while. It may inhibit CD1433 which sounds like a droid from Star Wars, but it inhibits this, that, or the other, and we don't know what that does until we knock it out and then we go, "Oh, that's what that does."

We know what it does in the tumor, but it also goes over here and does something we didn't see coming. So I think that that's been one of the other challenges. The other thing is if it moves, it gets a corticosteroid. The number of people on this witch's brew is just off the hook. Big doses of steroids; fludarabine, alemtuzumab; normally I'm not allowed to say these words at my institution. I go to the oncology pharmacist, I'm like, "You know, that one." But you've got all these other agents out there that result in some profound and different types of immunosuppression.

The infection rates are driven by neutropenia. One of the things that I want you to think about is the speed of the decline. When somebody's white cell count is dropping in a hurry, the speed with which that count is declining tends to oftentimes predict the duration of and the severity of the neutropenia. So when you see folks going down quickly, it's time to see if you can do anything about it and to have a very low threshold to start thinking about infections because, remember, a lot of immunosuppressed patients -- especially if corticosteroids are in play or other agents are in play -- a lot of the typical signs of infection that we think of may be masked.

We've got all these new drugs that we've talked about, we've got limited information in side effects and this four letter word that starts with C ends with S and has corticosteroid in between. It's a group of drugs that we need – we get so comfortable flinging big doses of steroids around that sometimes we forget exactly how immunosuppressive these agents could be.

So what do you do to prevent infections in these immunocompromised, complicated patients that you're taking care of? What about prophylaxis during neutropenia? Let's talk about this a little bit. The quinolones are the best-studied agents; they have the best data out there. They should not be used in low-risk patients. If you have patients with anticipated durations of neutropenia of less than or equal to 7 days, that means your solid tumor patients for the most part, don't be dropping fluoroquinolones on these people. Because those short durations or neutropenias are not typically where people get into trouble. We also know that the more you show folks quinolones, the more likely they are to colonize with quinolone-resistant stuff.

The NCCN recommendations right now suggest that you not go after these low-risk patients, but that the intermediate- and high-risk patients, folks who are expected to have neutropenias lasting longer than 7 days, or who have had problems with prior courses of chemo, with regards to infection and febrile neutropenia are the folks where we need to be thinking about quinolone prophylaxis and where there's pretty good data to support it.

I will be the first one to tell you that there's controversy in this area. There is a lot of question about, "Okay, at what point do we hit an E. coli rate with

quinolone resistance where the prophylaxis no longer works?" Nobody seems to know that answer right now, and there are a lot of institutions out there that are running 20 to 30% of their E. coli's being quinolone resistant. So this is an area where we have to keep an eye on the field and the data as it moves along.

The other thing, too, if you're dealing with stem cell transplant patients, I would highly encourage you not to forget about the pneumococcus. *Streptococcus pneumoniae* remains as nasty as it ever was, and penicillin prophylaxis is encouraged for out to a year in all allogeneic stem cell transplants. You want to make sure that it's continued until immunosuppression for graft-versus-host disease is complete. The antifungals we're not going to talk a lot about in the interest of time but, also, realize that this is something that needs to be thought about in particular in our allogeneic stem cell transplant group.

Other infections; pneumocystis, primarily be thinking about in folks with big doses of steroids. Also, temozolomide; brain tumor patients we see a lot of steroids going on there, thinking about PCP prophylaxis in those folks, greater than 20 mg of prednisone for 4 weeks, there's a surprising number of patients who meet that cutoff, and pneumocystis can be downright nasty when it does pop up. I already mentioned temozolomide a little bit, and remember radiotherapy does a nice job of whacking a lot of the bone marrow where your cells basically come from. This is an area where maybe we don't prophylax as many patients for this as we should. The antiviral prophylaxis, similar recommendations to up here, especially if folks have any incidence of HSV

infections or recent VSV infections. CMV is very problematic but primarily only for or mostly in our allogeneic stem cell transplant.

This is the area where I wanted to get to. This is an area that we need to be paying a lot of attention to. We've got good vaccines; we need to be using them. If we have people who we know are going to receive chemotherapy regimens, vaccinate them ahead of time. Even if you only get partial response, it's way better than no response, which is what you will get if you do not vaccinate them. There are very, very good guidelines; NCCN has them, IDSA has them. If you've not been to the IDSA website and seen the vaccination guidelines for high-risk patients, [idsociety.org](http://idsociety.org), look at the guidelines tab. There's really good stuff out there for who should be getting vaccines.

The other thing, though, is remember that some of these vaccines, such as varicella or zoster, all right, are live vaccines; you don't want to be giving live vaccines to people who are profoundly immunocompromised. So this is a really good thing to make sure you have a good reason to have that guideline document near you.

This right here is impossible to read, but what I want you to take away is this, the NCCN guidelines are full of really good tables like this. Go to [nccn.org](http://nccn.org) and look at this; nice, stepwise flowcharts here. What this is is the table talking about who can receive outpatient therapy for febrile neutropenia versus who needs inpatient management. This is all really nicely, clearly laid out. And a lot of our febrile neutropenia patients who are at low risk don't need hospitalization. What should you be thinking about, though, drug wise when you are presented

with someone who has febrile neutropenia? In the low-risk patients -- and, again, I would strongly encourage you to go to the NCCN guidelines and look at that definition for low risk -- the recommended regimen and the regimen I would encourage you to use is ciprofloxacin plus amoxicillin, clavulanic acid; otherwise known as Augmentin. The big thing with amox/clav -- don't ever dose this stuff BID in people with normal renal function. It needs to be three times a day. And remember that the ciprofloxacin dose here is three times a day as well.

I am not as big a fan of moxifloxacin because it doesn't have the pseudomonas coverage that ciprofloxacin has and it's maybe had some problems as compared to the other regimen. These are the agents that you want to be thinking about for intravenous monotherapy in inpatients; it's your cefepimes, your pip/tazos, and your meropenems; those are the places you need to be. Only be thinking about vancomycin in people who have Gram-positive infections, line sites that are pus'd out; we should not be hitting everybody with a big beta-lactam and vancomycin. Remember, vancomycin should be initiated in niche situations; gram-positive-driven-type situations.

When people are actively trying to die on you or are very hemodynamically unstable, you go with that Gram-negative coverage and you can consider adding an aminoglycoside for one or two doses while you figure out what's wrong. Because remember, the worst thing you can do in someone who is acutely septic is not have empiric coverage that gets the organism that eventually grows. You need to make sure that in patients who are septic that your first choice antibiotics cover the organism that you eventually grow.

To wrap it up, the biosimilars are coming; you now have four on the market. A lot of you have already seen filgrastim out there as a biosimilar. This is a really good thing; I think it will minimize expenses for our patients for our healthcare systems. The bugs, though, are increasingly problematic; you need to know what's going on in your institution. If you don't know where your antibiogram is, I want you on Monday to go find your antibiogram so you know what grows in your hospital and you know what your resistance rates are. Because I can tell you what's going on nationally, but you need to know what's going on in your institution.

And, again, appropriate prophylaxis and appropriate vaccination saves lives in profoundly immunocompromised patients or folks who are going to be immunocompromised for a long time. With that, I will thank you for being such a great audience after lunch. Have a great rest of your meeting.

**[END]**