Evolving Care Strategies in Newly Diagnosed Hodgkin Lymphoma

Emerging Therapies and the Changing Role of the Oncology Nurse

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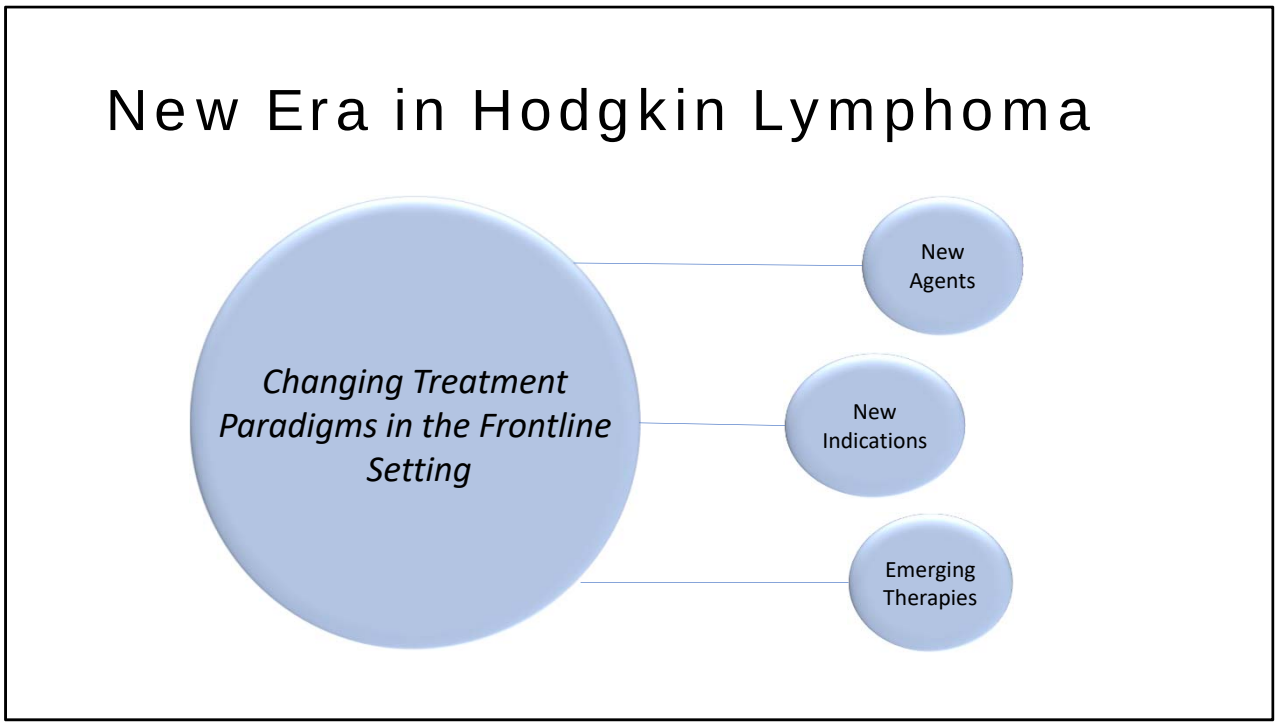

Amy Goodrich: We are really talking about changing treatment paradigms for frontline therapy of Hodgkin lymphoma. We have got new agents and new indications and emerging therapies. So there is a really a lot going on in Hodgkin lymphoma, so why do we care about Hodgkin lymphoma?

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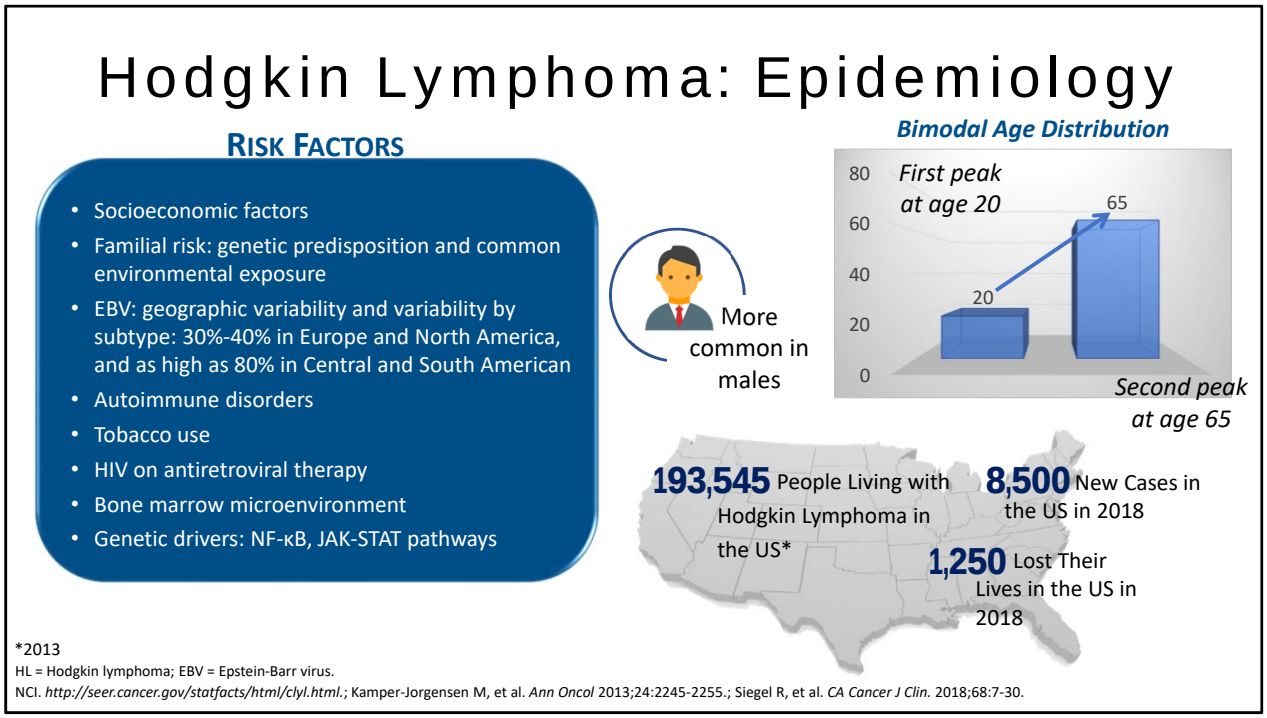
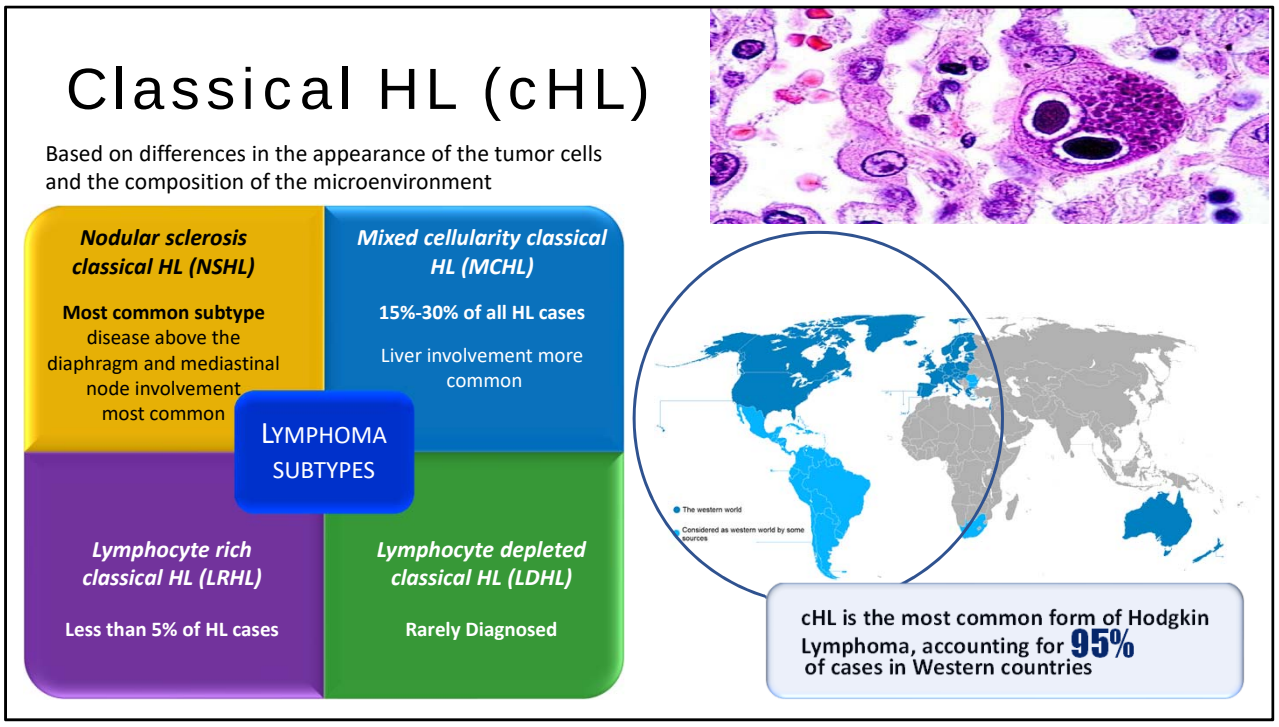
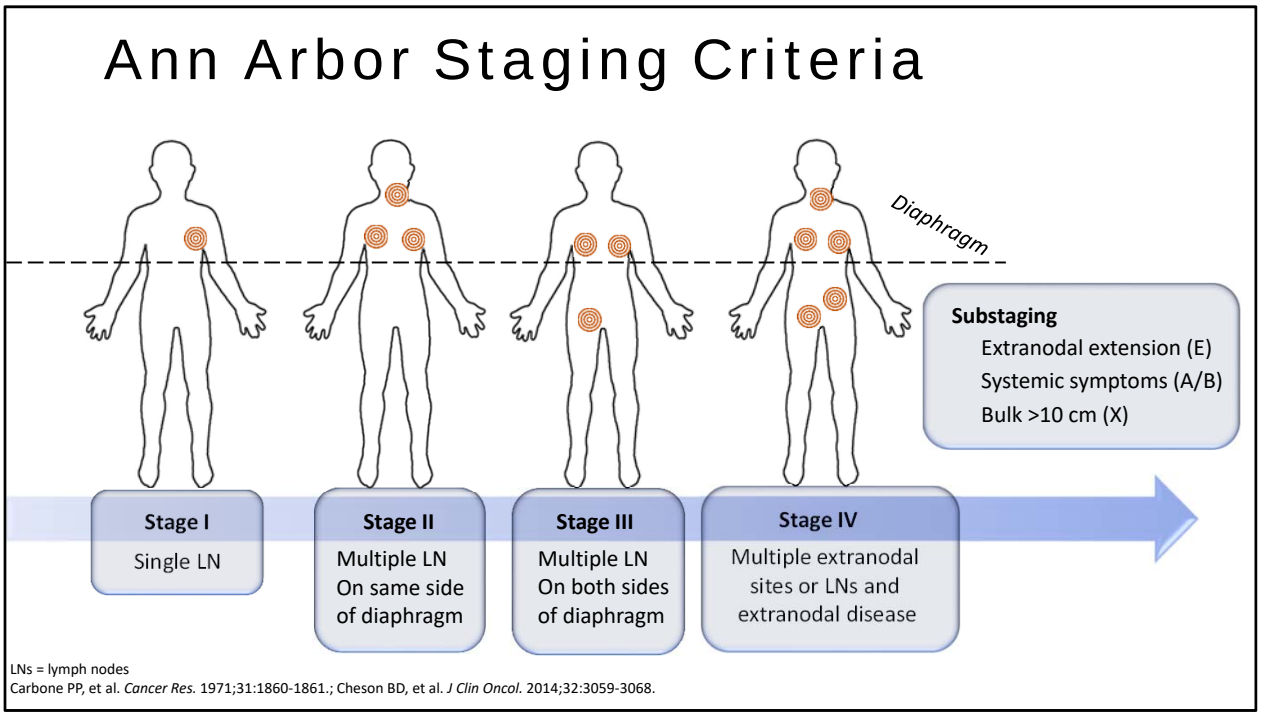


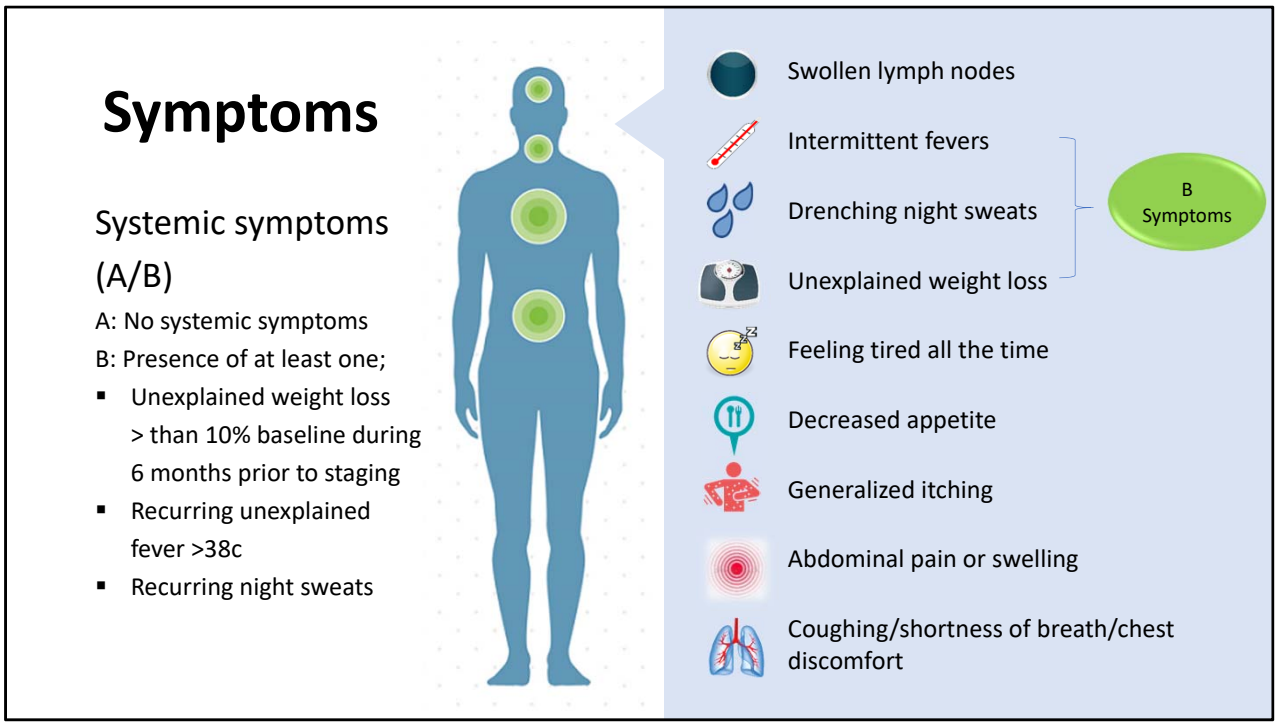
There are about 8500 new cases a year. This is still a relatively low volume disease, but as you can see there is two peaks, so this is a disease of the young and then again, it peaks as folks get older. If you look at, I love this statistic, there are almost 200,000 people in this country living with Hodgkin lymphoma, which is great. It is a great testament to the curability of this disease. Risk factors: there are socio-economic; there are some familial conditions that Hodgkin will run in families; viral, especially EBV; autoimmune disorders; tobacco use; HIV or antiretroviral therapy. There is some bone marrow disorders and some other genetic disorders, but really most patients do not have any of these risk factors.



Classical Hodgkin lymphoma is clumped into classical Hodgkin lymphoma or four separate subtypes of Hodgkin's, so nodular sclerosis or sclerosing, which is really the most commonly diagnosed Hodgkin lymphoma. Mixed cellularity is somewhere, 15% to 30%, and then very rarely do you have lymphocyte rich or lymphocyte depleted. So most of them are going to be nodular sclerosis or your mixed folks, but there are a couple of others as well. Classical, so these four together account for 95% of all Hodgkin lymphoma in Western countries, so this is really what you are mainly seeing.



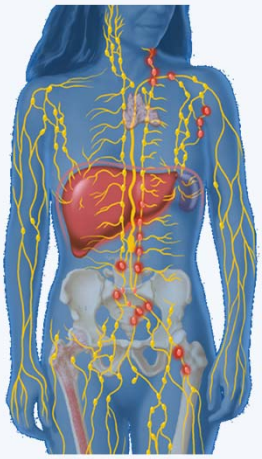
Staging for Hodgkin lymphoma is actually quite easy. For those of you who deal with that TNM horrible, complicated system. This is really easy. This is one of the easiest things about lymphomas in general, so Stage 1 is one node or one nodal region, so if somebody has three cervical nodes it is one nodal region. Stage 2 is multiple nodal regions on the same side of the diaphragm. Stage 3 is both sides of the diaphragm. Stage 4 is disseminated. This is usually bone marrow involvement. You might see an E for extra nodal. You might see an A or a B – A is no symptoms, B is having B symptoms, and this X for bulky, meaning over 10 cm.



In looking at symptoms, the A and the B, A means no symptoms and B means having at least one of the following: fevers of unknown origin to 38 degrees or higher, 10% body loss weight unexplained over the previous six months or recurring night sweats and this is not just your neck is a little sweaty. This is like head to toe drenching night sweats, but some of the other things that patients have, most patients, many come to diagnosis because they feel a lump, they feel tired, the anorexia, others are really classic having pruritus without rash so people are itchy, and with your 20-something year-olds, a lot of times alcohol will exacerbate them feeling itchy but having no rash. Patients can have abdominal pain and if they have mediastinum involvement, they can have trouble breathing or chest symptoms.

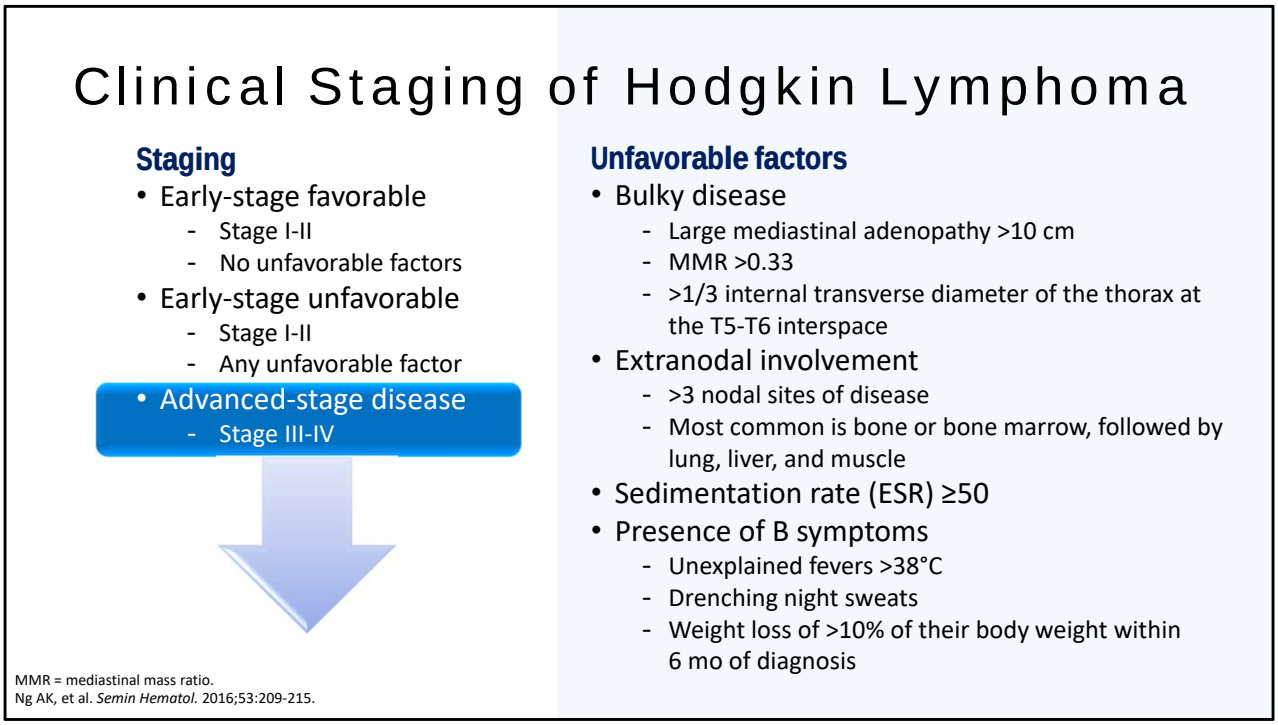
Patterns of Disease Presentation

- Contiguous spread most common in newly diagnosed patients; spread from node via lymphatic ducts
- Noncontiguous spread and hematologic distribution are more common with recurrent disease
- Rare patterns of presentation:
  - Rare to have HL in the neck and the lower abdomen without disease in the upper abdomen
  - Unusual to have bilateral axillary involvement without disease in the lower neck areas
  - Extremely unusual to have hepatic or bone marrow infiltration without disease in the spleen
  - Uncommon to have pulmonary disease at presentation without HL being present within the hilar lymph nodes, usually on the ipsilateral side



Rosenberg SA, et al. *Cancer Res.* 1966;26:1225.

Hodgkin is different than non-Hodgkin's, mainly, in many ways, not only the treatment and the prognosis but also how it spreads. Your non-Hodgkin's patients, they can have nodes anywhere and everywhere, Hodgkin tends to move contiguously, so it moves from nodal region to nodal region and does not really jump around the way the other lymphomas do. Rarely would you have a node in the neck and then another one in the abdomen or the pelvis without having something along the way also, it moves in a nice orderly pattern. Once patients have relapse disease, it is not such a predictable thing but certainly a diagnosis, so it is extremely rare to have hepatic bone marrow involvement without the spleen being involved, so again, there is some rhyme and reason to this, and so again, contiguous spread is the point of this slide.

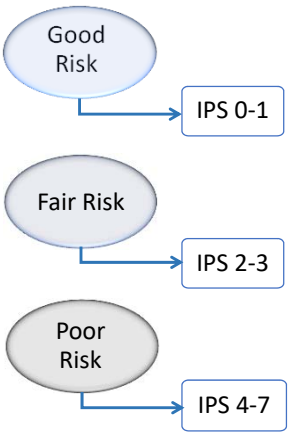


Staging, looking at prognostics based on staging. Early stage favorable patients have Stage 1 or 2 disease with none of these factors on the right, so bulky disease more than 10 cm. This MMR in the one-third, so this is about whether they have a mediastinal mass and does it encompass more than a third of their chest. This is pretty massive chest disease that patients can have. That is unfavorable. If they have more than 3 nodal sites. If their sed rate is elevated, also if they have B symptoms, so for folks who have early stage disease and none of those risk factors, they really do the best, and we well talk about this a little later, and then there is early stage unfavorable which is Stage 1 or 2 with any of these factors, and then Stage 3 and 4 which is where we are going to spend the bulk of our time. That is a high risk factor for patients to have that.

International Prognostic Score (IPS) for Advanced Stage Disease

1 Point for Each Factor

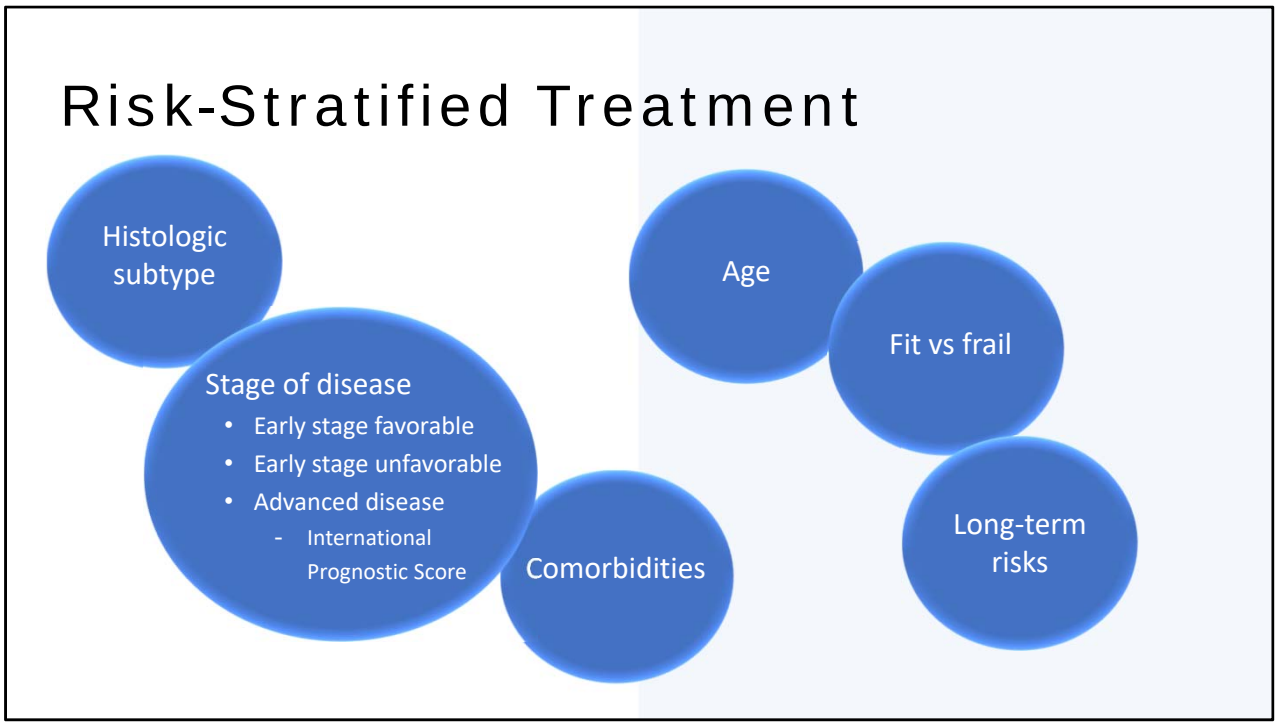
- ✓ Albumin <4 g/dL
- ✓ Hemoglobin <10.5 g/dL
- ✓ Male
- ✓ Age ≥45 yr
- ✓ Stage IV disease
- ✓ Leukocytosis (WBC >15,000/mm^3)
- ✓ Lymphocytopenia Lymphocyte count <8% of WBC and/or absolute lymphocyte count <600 cells/µL



Number of factors	PFS at 5 years (%)	% of patients
0	84	7
1	77	22
2	67	29
3	60	23
4	51	12
≥5	42	7

Hasenclever D, Diehl V. *N Engl J Med.* 1998;339:1506-1514.; NCCN guidelines 2018.

There is also this International Prognostic Score and this is really most useful for patients who have advanced-stage disease. You can see the factors, but really the take-home here is this matter is because if you look at the prognosis and the progression-free survival for these patients. Folks with none of these risk factors have an 84% progression-free survival at five years, we hate to say the word cure but these are really the people who are cured, and then if you have five or more, five and higher is really the most dismal patient population. It goes from about 80% to about 40% progression-free survival at five years, so these are the important factors, and then you can clump them into good, fair or poor based on how many points they have.



When you are looking at treatment and how to risk-stratify patients to choose their initial therapy, you are looking at what type Hodgkin they have. Do they have early favorable, what is their risk, what are their comorbidities, how old is this person, are they fit versus frail? You are also looking at long-term risks which we will talk about a little bit more later. Although there are not the huge varieties of treatments available for these patients, there are more coming and so customizing is becoming much more of a reality for these patients.

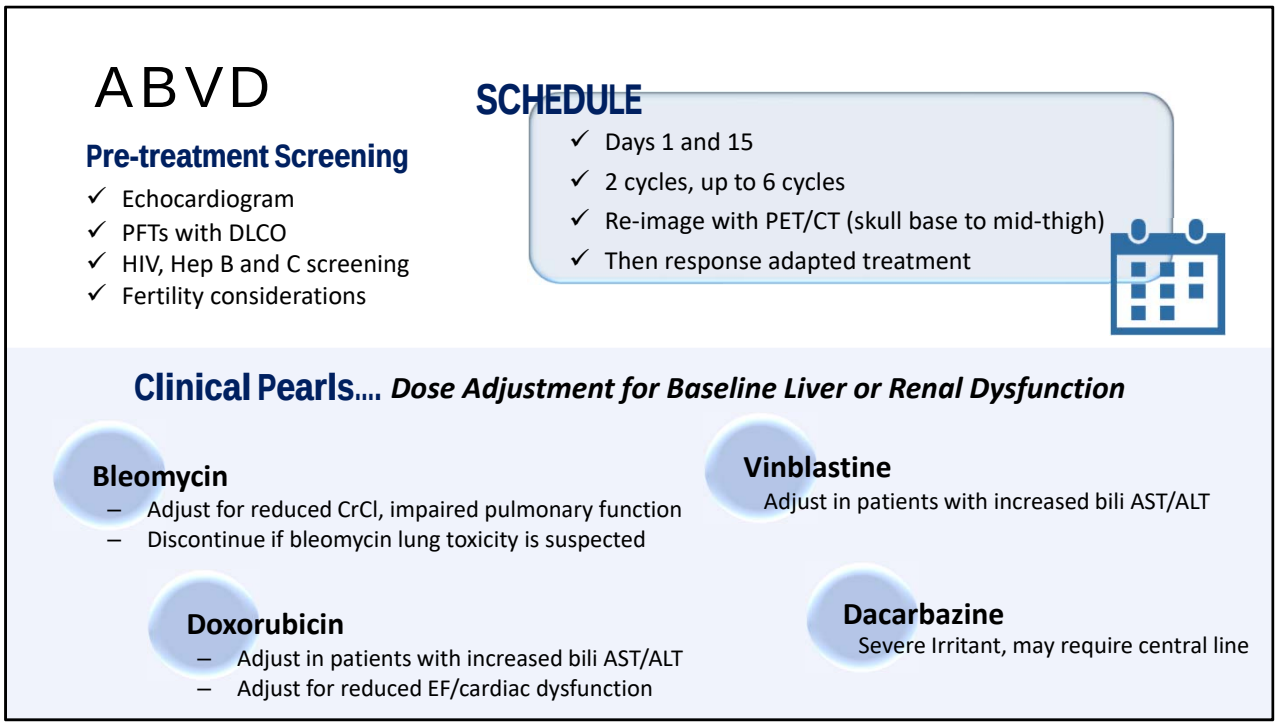
In looking at common regimens.

Common Frontline Therapies Used in cHL

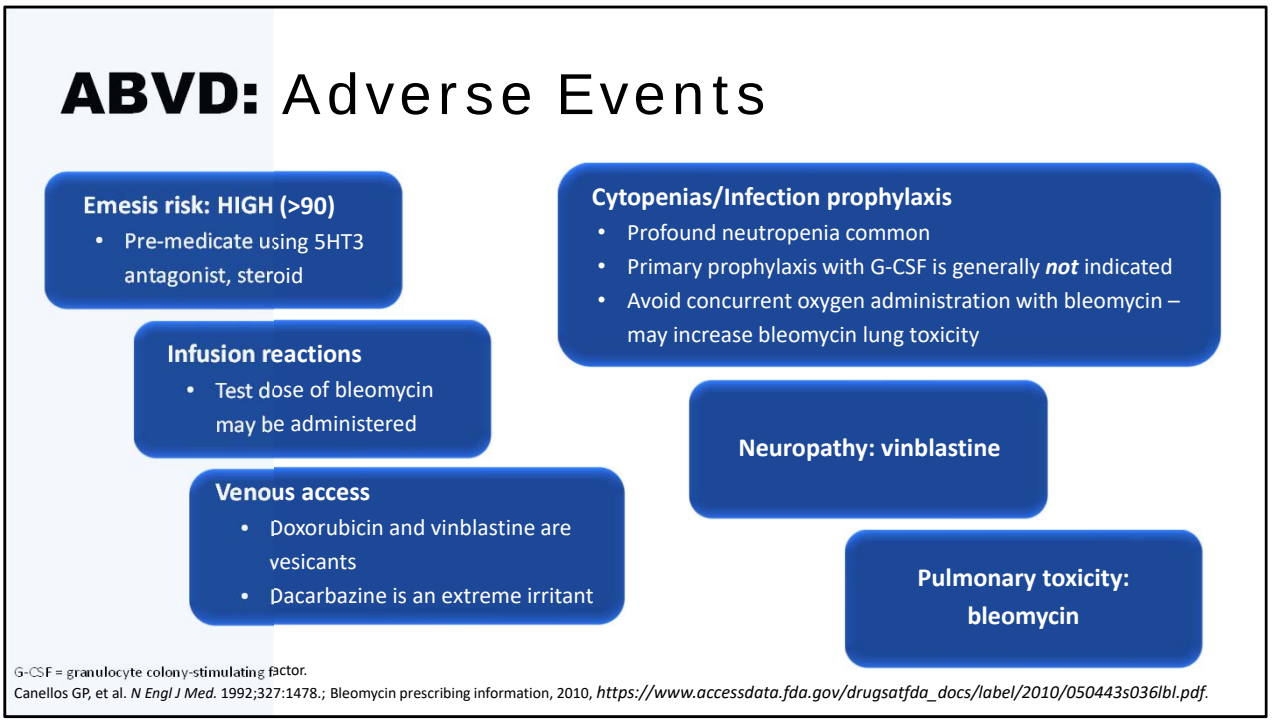
Regimen/Modality	Duration of therapy	Agents
ABVD	2-6 cycles	Doxorubicin 25 mg/m^2 IV Bleomycin 10 units/m^2 IV Vinblastine 6 mg/m^2 IV Dacarbazine 375 mg/m^2
Stanford V	8-12 weeks	doxorubicin, vinblastine, mechlorethamine, etoposide, vincristine, bleomycin, prednisone
BEACOPP	2-6 cycles	bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone
Involved site radiation therapy	Varies based on treatment location	
Brentuximab Vedotin (BV) + AVD	Up to 6 cycles	Brentuximab vedotin, doxorubicin, vinblastine, dacarbazine

NCCN Guidelines Version 3.2018 Hodgkin Lymphoma.; Engert A, et al. *N Engl J Med.* 2010;363:640-652.; Radford J, et al. *N Engl J Med*. 2015;372:1598-1607.; Raemaekers JM, et al. *J Clin Oncol*. 2014;32:1188-1194.; Eich HT, et al. *J Clin Oncol*. 2010;28:4199-4206.; Avandi RH, et al. *Ann Oncol*. 2013;24:1044-1048.; Gordon LI, et al. *J Clin Oncol*. 2013;33:1936-1942.; Engert A, et al. *Lancet*. 2012;379:1791-1799.; von Treskow B, et al. *J Clin Oncol*. 2012;30:907-913.; Connors JM, et al. *N Engl J Med*. 2018;378:331-344.

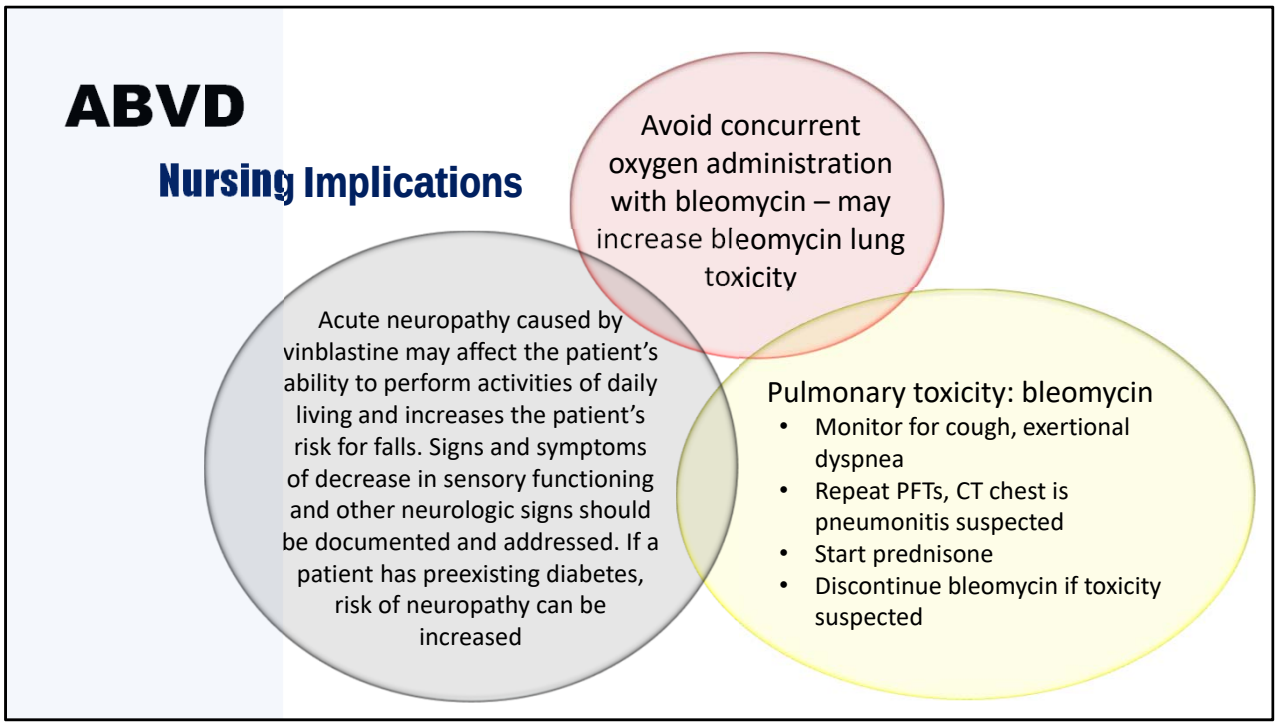
For initial therapy ABVD, everybody knows ABVD, right? We have all been working with ABVD for a long time, still a great regimen, still widely used in Hodgkin lymphoma giving 2 - 6 cycles depending upon a lot of factors. Stanford V which is also a multidrug regimen but has more drugs than ABVD, and that is given for 8 to 12 weeks. BEACOPP, again, this is multidrug. You can see there's some commonalities here. There is an anthracycline, there is a vinca, there are definitely common threads here, and then involved site radiation therapy is definitely much more commonly used in Hodgkin than non-Hodgkin's. Then the new player on the block is BV with AVD, so dropping off the bleomycin and adding BV for up to 6 cycles.



ABVD. Is everybody familiar with ABVD? We know this regimen. We love this regimen. We can get patients through this regimen, right? Days 1 and 15 between 2 and 6 cycles, you are going to re-imaged with PET after 2 cycles and then figure out where you are going from there, but before you treat any of these patients, because we looked at all those regimens, all of these regimens have an anthracycline, so people are going to need to have their echo done. Any regimen with bleomycin, you have to be worried about PFTs, HIV, hepatitis, hep-C, this is not unique to ABVD. This is with any of these regimens that you are going use upfront, and also fertility considerations. Again, you have got the 20-year-old peak and then the 65-year-old peak so you have got to think about the folks who are in their fertility years. Dose adjustments are here. The bleomycin gets dose reduced if there is impaired pulmonary function or reduced creatinine clearance, and then you are going to get rid of the bleomycin very quickly if people develop lung toxicity. The doxorubicin, you are looking at LFTs and cardiac function. For the vinblastine, AST, ALT dose reductions, and the dacarbazine is the one that burns people. You guys know this when you are giving it, it burns them. I think that most people can get through this without needing a central line but you have to keep that in the back of your mind too.



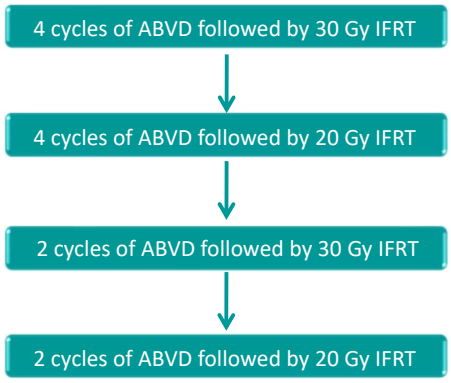
Adverse events, we are all familiar with ABVD. We know this is a high and metagenic potential regimen so using your 5-HT3 drugs, it is not uncommon for these people to need aprepitant or fosaprepitant needing to even go up from there. Folks can have infusion reactions with bleomycin. If you guys see this frequently, it is a pretty uncommon thing but you need to know that it is a possibility. Again, venous access, so the really unique thing about ABVD is you know these people, their counts, they bottom out, they come back up. You are treating them when they are neutropenic. It is sort of amazing that they have such low counts over and over and over again and they really have very low infection rate, so this profound neutropenia is very common. Typically do not use growth factors with these folks, and then you just need to be careful about not giving people oxygen while they are getting bleomycin because that can exacerbate the lung toxicity. You are always looking for neuropathy. Any time you have one of those vinca's and then, again, pulmonary toxicity with bleomycin.



The neuropathy, every time you treat these patients, we should all be asking about neuropathy and making sure that they are not having an impact on their activities of daily living which does prompt dose reductions or dose omissions. Again, lots of these older folks in that second peak, they are going to have neuropathy walking through your door, so getting a really good baseline is critical. I know that there are tools out there, some practices to use these tools, some do not, whatever you use is fine as long as getting it done. You have got to know at baseline really what their neuropathy status is. We talked about the oxygen with bleomycin, but anybody getting bleomycin, you really also needing every dose asking about cough, dyspnea on exertion, this is very physician driven, it's preference, how often you do pulmonary function studies, how often are you really monitoring these people other than symptoms and there is really no right or wrong as long as this is getting done. If you suspect bleo toxicity, you are going to do some imaging, some pulmonary function studies. If it is, you are going start prednisone and likely discontinue the bleomycin completely.

German Hodgkin Study Group (GHSG) HD10

Randomly assigned 1,370 patients with favorable prognosis early-stage HL:



At a median follow-up of 7.5 years:

Outcome	2 cycles of ABVD	4 cycles of ABVD
5-year OS	96.6%	97.1%
PFS	91.2%	93.5%
FTF	91.1%	93%
8-year OS	94%	95%
Grade 3/4 AEs	33%	52%
Leukopenia	15%	24%
Infections	1.7%	5.1%
Hair loss	15%	28%

IFRT = involved-field radiation therapy; AEs = adverse events; OS = overall survival; PFS = progression-free survival; FTF = freedom from treatment failure.
Engert A, et al. *N Engl J Med.* 2010;363:640.

I love this study. Our cream of the crop Hodgkin people you saw there is an 84%, that was for advanced stage, so the early stage people, it is even higher than that. We cure the vast majority of these people, so the German Hodgkin Study Group did this trial and said, “Okay, do people need 4 cycles, do they need 4 cycles at all?” Early stage disease typically also get involved field radiation, so they were looking at how much radiation do these folks need? How many cycles of ABVD do these patients need because all of these things have long-term toxicities associated with them. There were four arms here, 2 cycles of ABVD with two different radiation doses and the same with 4 cycles of ABVD. They quickly figured out the radiation part does not make a difference, so the 20 was just as good as the 30. But I love this, 2 cycles of ABVD versus 4. If you look at the five-year overall survival, they are really identical, 96.6 versus 97.1. So again, these are toxic drugs. If you can get away with giving the least amount possible and maintain those exceptional outcomes, it is definitely worth it. Again, these are typically either very young people who are in college or starting their jobs or starting families, or they are older folks with lots of comorbidities. So, these 2 cycles in radiation hopefully you are seeing more that for your early stage good-risk patients.

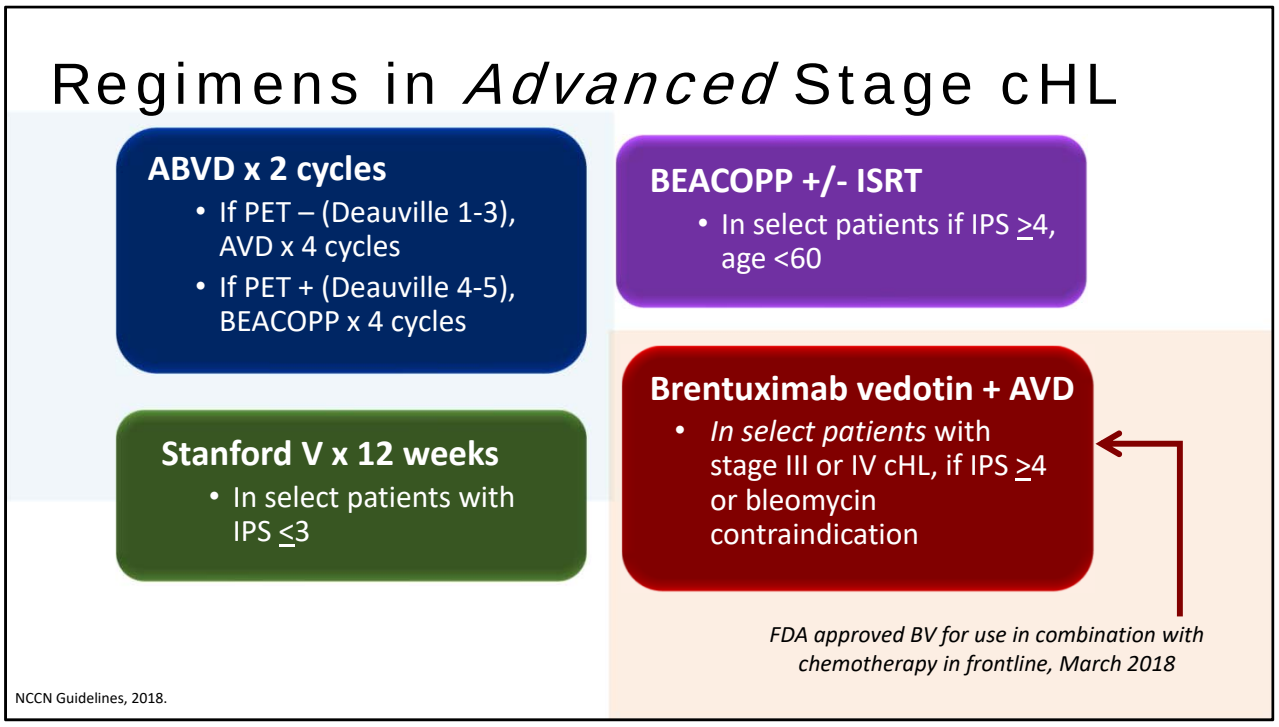
Response Adapted Frontline Therapy Deauville Criteria, PET 5-Point Scale

- Maximize cures while minimizing late effects
- Avoid undertreatment **or** overtreatment
- Reduce treatment emergent adverse events
- Reduce potential long-term effects including secondary malignancies

Score	PET/CT Result
1	No uptake
2	Uptake ≤ mediastinum
3	Uptake > mediastinum but ≤ liver
4	Uptake moderately higher than liver
5	Uptake markedly higher than liver and/or new lesions
X	New areas of uptake unlikely to be related to lymphoma

Barington SF, et al. *J Clin Oncol.* 2014;32:3048-3058.; Hutchings M. *Hematology Am Soc Hematol Educ Program*. 2012;2012:322-327.; Johnson PW. *Hematology Am Soc Hematol Educ Program.* 2016;316-322.

The concept of PET scans and actually switching therapy based on PET scans or PET scans driving therapy, really are coming in to play in Hodgkin lymphoma. Hopefully you all know this, PET scans, it is not a yes or no, it is a 1 through 5 system. The Deauville score, the Deauville criteria and, hopefully, when you are reading PET scan results you are seeing this, so 1 to 3 is considered negative and 4 to 5 are considered worrisome or positive for sure.



In advanced Hodgkin now you give people a couple of cycles of ABVD and this is what is most commonly being done. You get a PET. If it is negative, meaning 1 through 3, you just finish out the ABVD. If it is positive, you switch to BEACOPP. So you are taking those patients who do not have a negative PET scan after 2 cycles and you are going to do something different. For advanced-stage disease, you can also just give BEACOPP if their IPS score is high and they are less than 60, and I will show you why in a minute. Stanford V also can be used for 12 weeks in advanced-stage disease with an IPS score of 3 or below, and then the new player here is BV with AVD. Has anybody given this yet? Great, okay. In vey select patients with advanced-stage disease, high IPS scores or if they have a bleomycin contraindication. These are your COPD patients, your emphysema patients, we have lots of elderly folks on oxygen or teetering on the brink of pulmonary disaster for lots of reasons. These are people who you would really not want to give bleomycin to, so this is a great new option, BV with AVD.

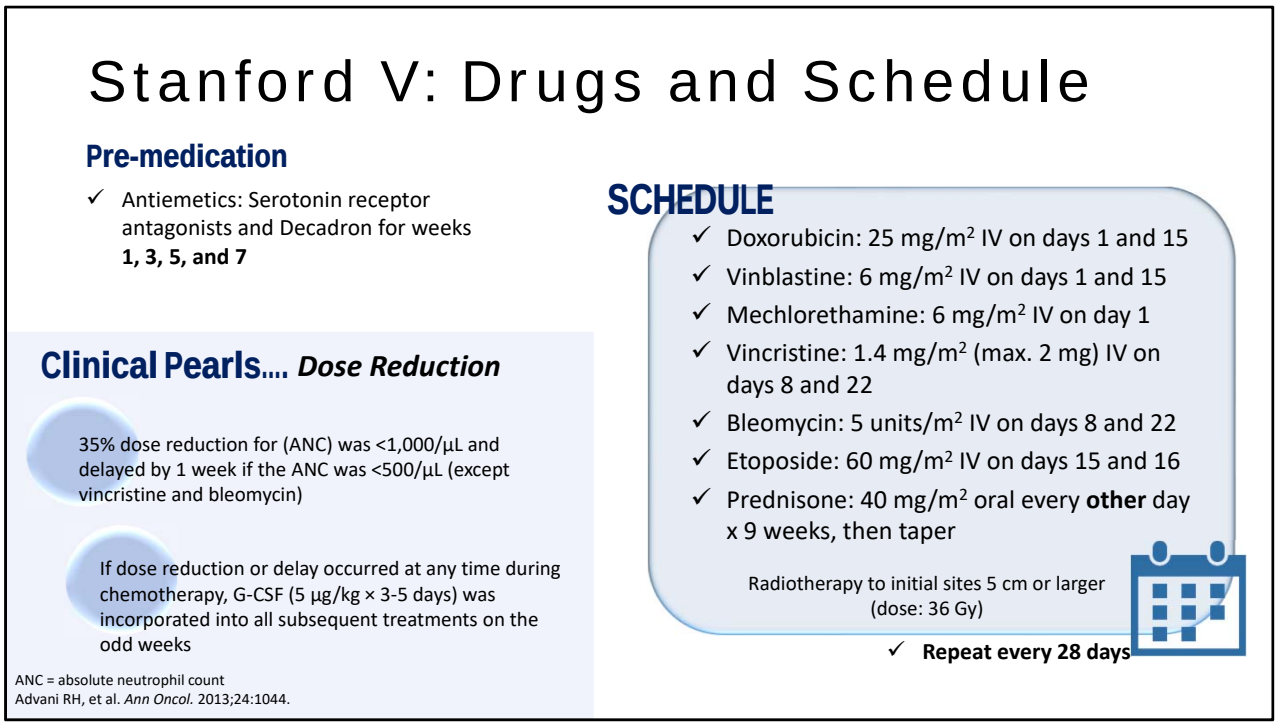
Toxicity and Efficacy of Regimens used in Locally Extensive and Advanced Stage cHL

Regimen	Common toxicities (Grade 3 or higher)	Efficacy
ABVD	Neutropenia 76% Neuropathy 5%	CR 73% FFS 74% at 6.4 years
Stanford V	Neutropenia 70% Neuropathy 16%	CR 69% FFS 71% at 6.4 years
BEACOPP	Leukopenia 88% Neuropathy 5%	CR 94% PFS at 5 years 90%
BV + AVD	Neutropenia 54% Neuropathy 9%	CR 73% PFS 82% at 24.6 months

CR = complete response; FFS = failure free survival; PFS= progression free survival

Gordon LI, et al. *J Clin Oncol.* 2013;31:684-691.; Engert A, et al. *Lancet.* 2012;379:1791-1799.; Connors JM, et al. *N Engl J Med.* 2018;378:331-334.; Hoskin PJ, et al. *J Clin Oncol.* 2009;27:5390-5396.

Looking at the toxicity, and I just pulled out neutropenia and neuropathy here and efficacy, so we are very used to ABVD, high neutropenia, low neuropathy, really good complete response rates. Stanford V has about the same neutropenia, more neuropathy because they get vincristine and vinblastine in Stanford V, complete response rate of about 70%. BEACOPP again, we had a complete response rate of 94% with very similar toxicity but we are going to talk about BEACOPP, and then ABV and AVD, again, complete response rate of about 73%. A little less neutropenia, but then there is a real neuropathy rate with that regimen.



When looking at Stanford V, has anybody giving Stanford V commonly? These do tend to be the one-off patients. It is a very aggressive regimen here and you can see the vinblastine and vincristine, and they are getting something all the time. This is a really aggressive regimen. There are lots of dose reductions for neutropenia, use growth factor with this regimen, so this is a tough regimen but it is actually a very good regimen for these folks, so an option.

BEACOPP

Age and PS-Adjusted Treatment-Related Mortality

- <40 years with ECOG PS <2 (2,164 patients) = TRM 0.7%
- <40 years with ECOG PS ≥2 (108 patients) = TRM 0.9%
- 40 to 49 years with ECOG PS <2 (592 patients) = TRM 1.7%
- 40 to 49 years with ECOG PS ≥2 (40 patients) = TRM 15 %
- ≥50 years with ECOG PS <2 (453 patients) = TRM 5.7%
- ≥50 years with ECOG PS ≥2 (45 patients) = TRM 13.3%

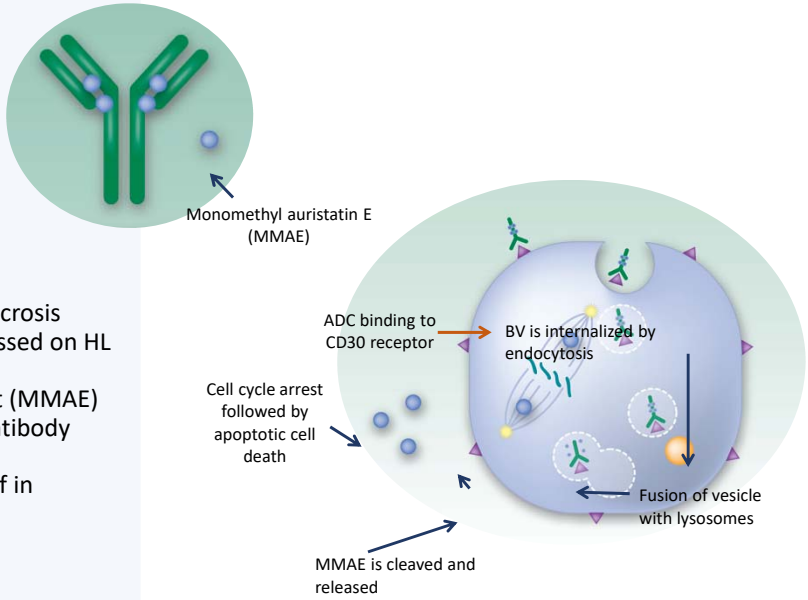
Drugs	Escalated BEACOPP	Standard BEACOPP
Bleomycin	10 units/m^2 IV on day 8	10 units/m^2 IV on day 8
Etoposide	200 mg/m^2 IV on days 1-3	100 mg/m^2 IV days 1-3
Doxorubicin	35 mg/m^2 IV on day 1	25 mg/m^2 IV on day 1
Cyclophosphamide	1,250 mg/m^2 IV on day 1	650 mg/m^2 IV on day 1
Vincristine	1.4 mg/m^2 (max 2 mg) IV on day 8	1.4 mg/m^2 (max 2 mg) IV on day 8
Procarbazine	100 mg/m^2 oral day 1-7	100 mg/m^2 oral days 1-7
Prednisone	40 mg/m^2 oral days 1-14	40 mg/m^2 oral on days 1-14
G-CSF	SC starting on day 8	

ECOG = Eastern Cooperative Oncology Group; PS = performance status; TRM = treatment-related mortality; SC = subcutaneously.
Wongso D, et al. *J Clin Oncol.* 2013;31:2819-2824.

In talking about BEACOPP and why giving 2 cycles of ABVD and making someone have a positive PET scan before you switch them to BEACOPP. If you look at this on the left side, if you look at folks who are under 40 or up to 49 years old, if you look at the treatment related mortality, 1.7 is the highest. But when you go into that blue block, so patients 40 to 49 with an ECOG Performance Status of 2 or greater, so these are people who are in bed half the day or more because of symptoms of their disease. The treatment related mortality goes up to 15%, those are transplant rates of mortality. If people are over 50 regardless of their performance status, their treatment related mortality is also high either about 6% or 13% or 14%. This is one of the reasons you are not using BEACOPP like water again because in older folks, this is really a tough regimen, but if folks are not getting into that PET negative complete remission with ABVD, then doing 4 cycles is less toxic. This reflects all 6 cycles.

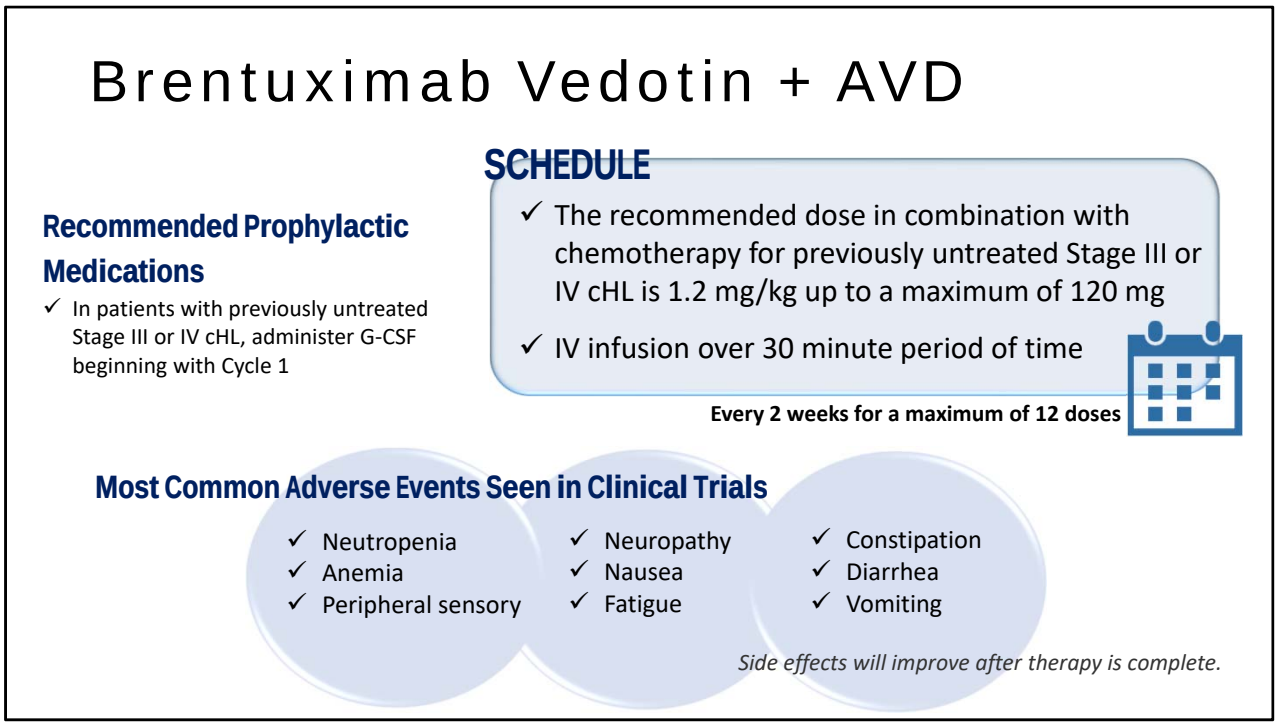
Brentuximab Vedotin

- Antibody drug conjugate (ADC)
- Targets CD30 expressed on RS cells
- CD30 is a member of the tumor necrosis factor receptor family and is expressed on HL
- Combines potent antitubulin agent (MMAE) with CD30 chimeric monoclonal antibody
- Linker ensures minimal drug fall-off in plasma

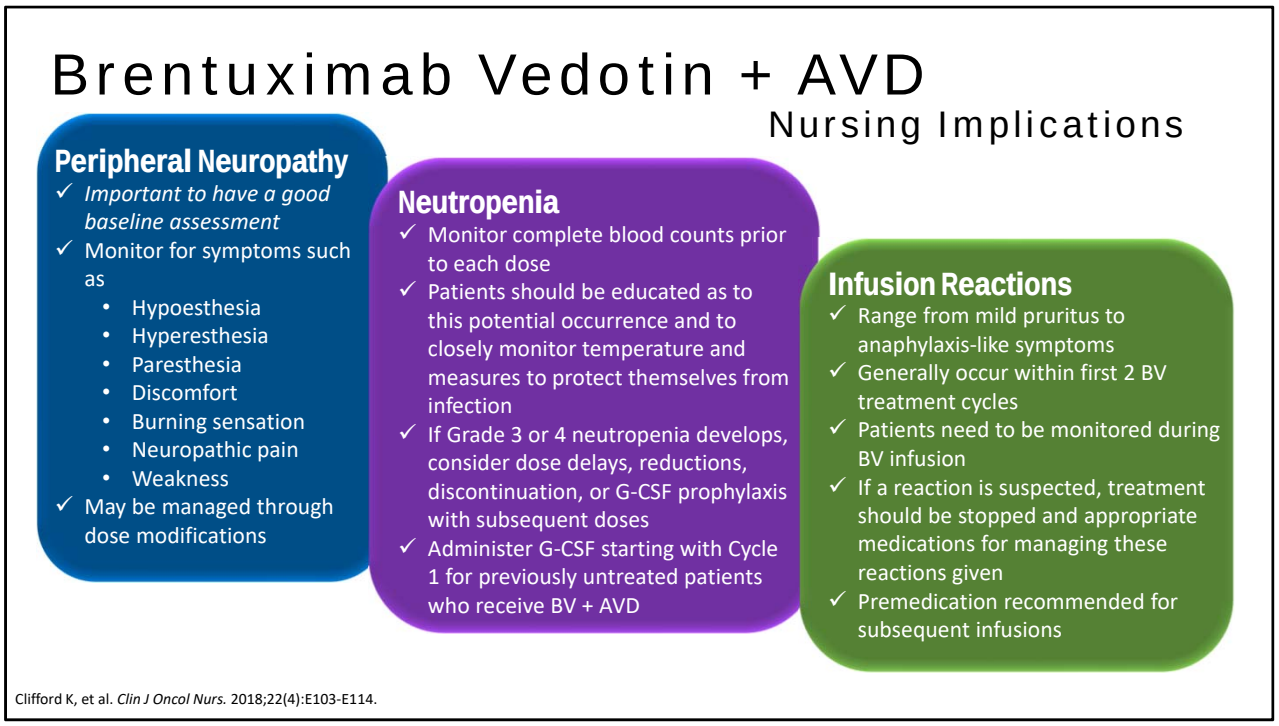


Shustov A. *Ther Adv Hematol.* 2013;4:173-187.; Deng C, et al. *Clin Cancer Res.* 2013;19(1):22–27.

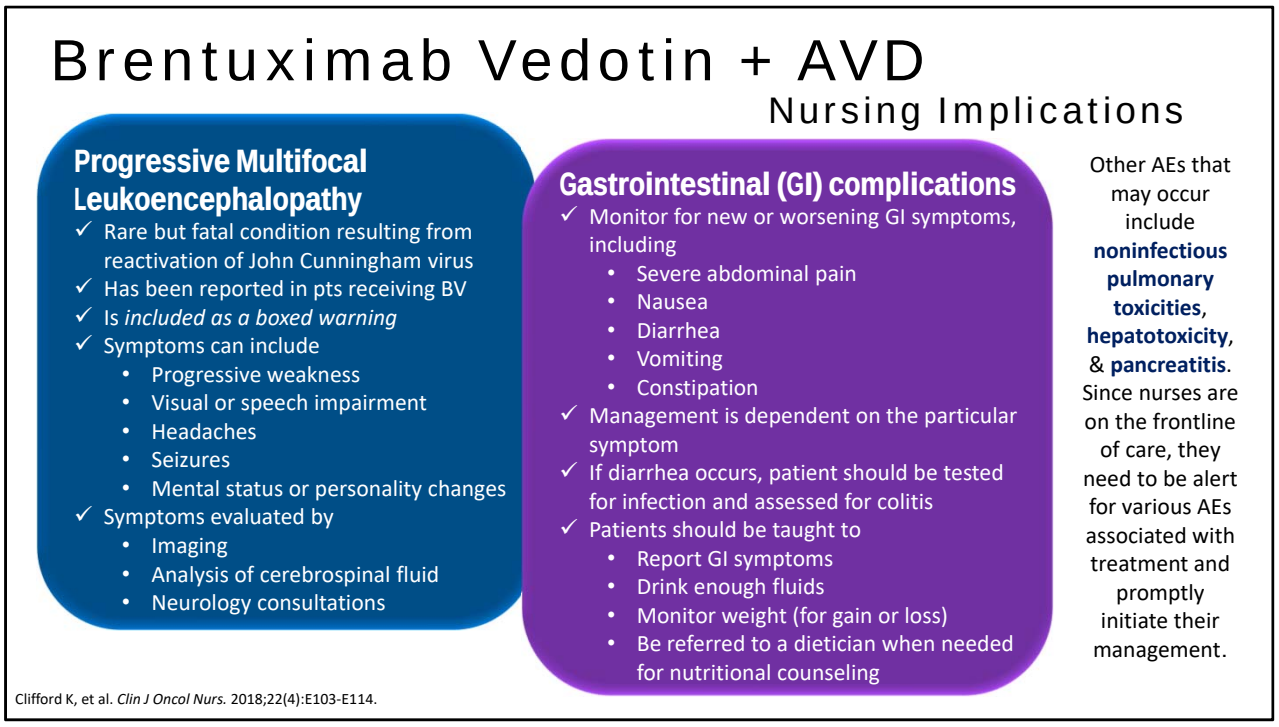
BV, is everybody giving brentuximab vedotin? You are giving it for lots of things, right? So in the frontline setting is what we are focusing on. BV is a conjugate, so it is a monoclonal antibody that hooks on the CD30, which is part of the Hodgkin morphology or one of the targets. MMAE is a drug that really, about a decade-and-a-half ago, maybe two decades ago now, was given systemically. It was highly effective against malignancies of all sorts, but the toxicity was completely devastating and unacceptable. So somebody got really smart and figured out how to hook this MMAE great little toxic bomb onto an antibody and have it go right into the cell. So instead of pumping through your bloodstream, it now, it goes right into the Hodgkin cell and really does not reek that mass havoc that it does when you give systemically. So this was a really good drug that it is now usable.



BV with AVD, again, in patients, really advanced stage patients who you do not want to give bleomycin to or if you do not want give bleomycin to a patient. The recommended dose in other indications is 1.8 mg per kg, so this is little lower because you are giving it with in a combination regimen. You are looking for neutropenia, anemia, the rate of peripheral neuropathy, sensory and motor is about 60% for patients getting BV, so that is definitely something that you need to be asking about. Then as you can see, lots of GI toxicity of all flavors there with BV.



So again, you are looking for neuropathy. It can be sensory or motor about a little over 50% of what you are going to see, 53% of patients will have sensory and about 7% will have motor, so sensory high and motor are little lower. Neutropenia, you are going to monitor blood counts, you are going to consider dose delays or reductions if patients develop profound neutropenia, and then you are also going to consider growth factor for those patients as well. Patients can have infusion reactions with brentuximab. It is a monoclonal antibody, so you are going to do all the things that you do with all your other monoclonals that you are giving all the time, all day long for those of you who work in infusion areas just making sure you are monitoring patients, you have your emergency equipment around and you stop it, you do the right thing like you do with all your other antibodies.

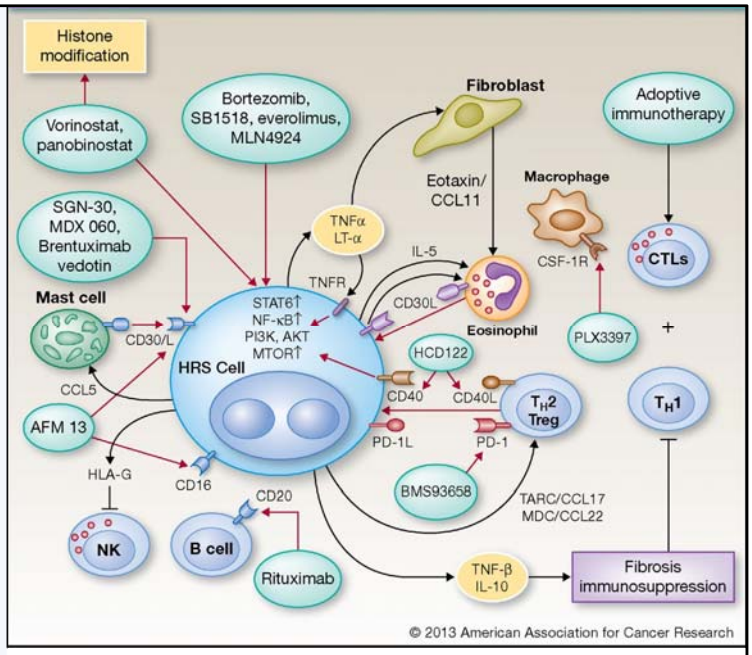


PML is also seen with this regimen and this happens very rarely but we all need to be looking for this. It is caused by reactivation of JC virus. It is in their black box warning for brentuximab and people can have all sorts of neuro symptoms, hopefully, you have never seen this. When you do, you never forget it. It is usually progressive. Usually starts with weakness or just some subtle impairments and it really can progress to seizures and personality, mental status changes, and can be fatal. If you think someone has this, you are going to be imaging their head. They are going to get an LP done. You are going to get neuro in. This is really a sort of an all hands-on deck issue when it happens. So again, GI complications, we talked about this, there could be nausea, vomiting, constipation, diarrhea, whatever it is, you are going to do supportive care, so you are monitoring counts, neuropathy and GI symptoms mainly for anybody getting brentuximab.

HL and the Microenvironment

Potential Therapeutic Targets

Tailoring the therapy to the tumor biology of the patient may improve outcomes



Diefenbach C, Steidl C. *Clin Cancer Res*. 2013;19(11):2797-2803.

This is kind of a busy slide, I am sorry about this. This is really showing you the Hodgkin microenvironment, and if you just look at this for a couple of seconds and look at all those familiar targets and all the places that drugs can potentially be active in Hodgkin lymphoma, so we now have pulled brentuximab into first line. You are going to see more of these new pathways and novel agents getting pulled in, and probably combined with other active drugs in Hodgkin, so I think the BV plus AVD is just a tip of the iceberg for the new drug plus our old favorite drugs for this disease.

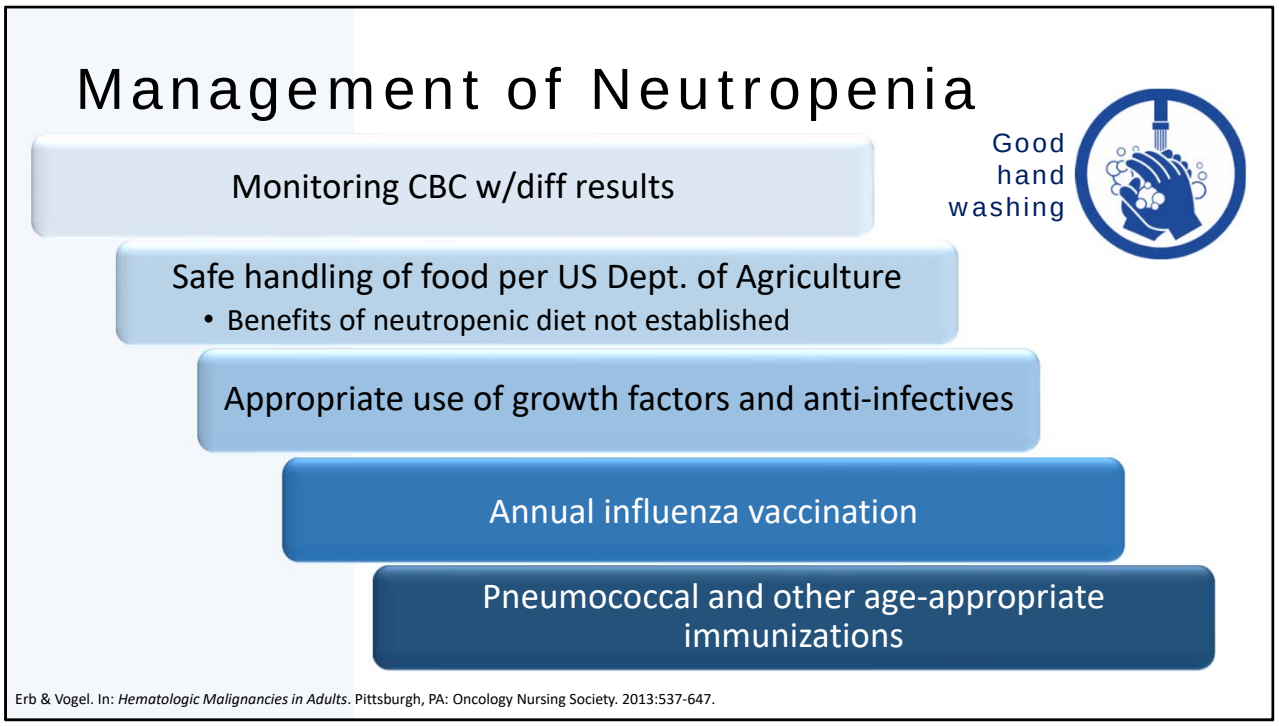
Novel Agents in the Treatment of cHL

Drug	Drug class	Target
Receptor-targeting therapies		
Brentuximab vedotin	ADC	CD30
Nivolumab, pembrolizumab	MoAb	PD-1
Rituximab	MoAb	CD20
Galiximab	MoAb	CD80
Microenvironment-targeting therapies		
Lenalidomide	Immunomodulator	T cells, NK cells, Tregs
Panobinostat	HDACi	HDAC
Mocetinostat	HDACi	HDAC
Inhibitors of signaling pathways		
Everolimus	mTOR inhibitor	mTORC1
Perifosine/sorafenib	AKT/MAPK inhibitor	AKT/MAPK

ADC = antibody-drug conjugate; MoAb = monoclonal antibody; NK = natural killer; HDACi = histone deacetylase inhibitor; mTOR = mechanistic target of rapamycin.
Diefenbach C, Steidl C. *Clin Cancer Res.* 2013;19(11):2797-2803.

This is some of the novel agents that are either here or under study or on the verge of coming. We have got brentuximab, nivolumab and pembrolizumab are used after first line, so they are used second line and beyond. We have got our lenalidomide and some HDAC inhibitors, then we have got mTOR inhibitors, and we have got things like sorafenib which has been around for a long time, but really looking at pathways that we have drugs that are active and then finding new drugs for pathways that we do not have drugs for.

Molly Moran: As Amy had presented to us the all the different regimens that are available for Hodgkin's, the treatment of Hodgkin's lymphoma, my job is to talk about how do we manage the side effects. These are folks who are coming into the office frequently. They make frequent phone calls. They have got a lot of life stressors that are happening around them, and our job as healthcare providers and their healthcare team to make sure that we can get then through. One of the first things we will talk about is neutropenia. This is not news. This is something that we have been working with for many years and dealing with the side effects of neutropenia.



One of the first things you do is good handwashing, right? Wash your hands, wash your hands, wash your hands, tell the patients. They always say, “What can I do to make my counts better? What can I do to make myself safe?” Wash your hands, wash your hands, wash your hands like you cannot say it enough, and they should be carrying around s big bottle of Purell, it should be hanging off there, they should have one on each hip and they should be like, pfft. Any teacher should have a big one on their desk, if you cross this line, you have to touch this, right? But one of the most important things we can do is know if they are neutropenic, so monitor CBC, safe-handling of fruits and vegetables and agriculture. The benefits of neutropenic diet are not so clear as they used to be. I still work with a lot of infusion nurses who drill that into folks heads--you cannot eat a fresh fruit or vegetable. We live in the northeast part of the country and there is only two months of the year where you can get a fresh tomato, and if you think I am telling someone that they cannot eat a fresh tomato during tomato season, you are crazy. Wash it. If you can peel it, you can eat it, right, so, wash it, wash it, wash it. All those kind of good things. Use growth factors and anti-infectives when appropriate. This time of the year, flu shot, everybody get your flu shot, and pneumococcal vaccines and other age-appropriate immunizations. Things like TDAP and whatever they call it. Whooping cough.

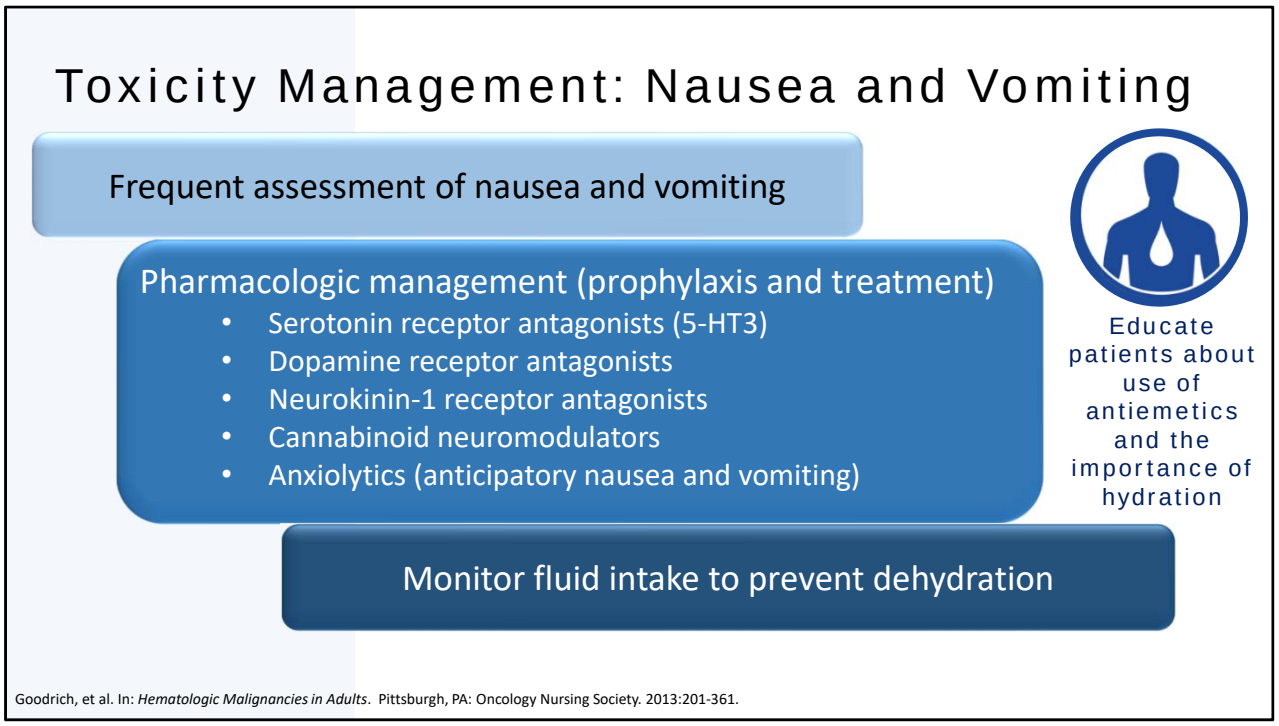
Antimicrobial Prophylaxis

Type	Population	Recommendation	Timing
Antibacterial	High risk for febrile neutropenia or protracted neutropenia	Fluoroquinolone prophylaxis	During period of expected neutropenia
Antiviral	HSV-seropositive undergoing HSCT	Nucleoside analog prophylaxis (eg, acyclovir)	Until WBC recovery or extended dosing
	Substantial risk of HBV reactivation	Nucleoside reverse transcription inhibitor (eg, entecavir)	Baseline, ongoing monitoring
	Any treated cancer patient	Inactivated influenza vaccine	Annually
	Immunosuppressed adult oncology patient	Follow guidelines (CDC, IDSA)	Before cancer treatment, household members
Antifungal	High risk for febrile neutropenia or protracted neutropenia or GVHD	Oral triazole, mold-active triazole for highest risk (GVHD)	During period of expected neutropenia
	Chemo regimens with >3.5% risk for pneumonia from Pneumocystis jirovecii (eg, purine analogs, daily steroids for >1 month)	Trimethoprim-sulfamethoxazole	Until engraftment after HSCT and/or treatment of GVHD

ASCO Guidelines, 2018.; Rubin LG, et al. *Clin Infect Dis.* 2014;58:e44-e100.

I will tell you there are antimicrobials that we think about as prophylaxis. Sometimes, if you know a patient is at high risk, they have got a line, they have a history of gram negative sepsis or something you can sometimes give them a fluoroquinolone to do some prophylaxis as you are going along. Oftentimes, we do not with ABVD. As Amy said, as stinky as their counts are over and over and over, they have a low incidence of febrile neutropenia. They have lots of neutropenia but not so much on the side of the infection and it is this quick bouncing up and down of their counts and the recovery of their neutrophils but a lot of times, you will fire them right into the next cycle even when they are on the brink of, when they are borderline neutropenic. It is not something we get too excited about in upfront ABVD. Antiviral prophylaxis we think about things like if they have a history of shingles. If they have a history of hep-B or hep-C, we think about treating those things. In our practice it is mixed about whether you do shingles vaccines or not. Now that they have the non-live version, it is probably okay, but in some of the B-cell malignancies, maybe not so much in Hodgkin's disease, you are not exactly sure how they are going to respond or if they are going to mount a response to it and so that is maybe where the question mark comes in. You are not going to hurt them, they are not going to get reactivation but they may have trouble with that. Then again with the hepatitis's, if they have hepatitis B positivity, you can treat the hep-B and still treat them on chemotherapy and get them right through, and then antifungal therapy.

Patients who have things like high neutropenia, risk, graft versus host disease. Those are folks who get put on to antifungal medicines and then certainly, treatment for PCP pneumonia or PJPs, it has now been deemed but not so much in Hodgkin's disease. These are not things that we commonly see in the Hodgkin's patients. Certainly, once we talked about transplant and relapse, then those become different processes and someone who is going to be on high dose steroids you think about all these right away. So if you are going to be on steroids for a month, you start to think about these prophylactic potentials.



Nausea and vomiting. These are two separate entities. We are really good at treating vomiting. I think we still lack a bit in treating nausea because people may not be throwing up all the time but they are still feeling just yucky, and so treating both I think is very important. We have so many drugs that we did not have when I started. There is the serotonin receptor antagonist, the 5-HT3's, I am not going to go through this, as oncology nurses we know algorithm after algorithm that is printed on a card that you have in every lab code, every pocket, every locker, every lunchbox that you have ever owned has an algorithm on it. Now we are getting into the cannabinoids and the legalization of marijuana and how does that affect our patients--not today's talk, another talk we will sit down and maybe do that. But again, some of these work on nausea, some of them work on vomiting, and so make sure that you have covered all and as Amy said, add things, layer things, these are high emetogenic therapies and they can interfere with quality of life and compliance as well. Monitor fluid intake to preserve hydration status. If you get nauseous, you do not drink enough, if you are dehydrated, it causes nausea. If you do not drink enough, you get dehydrated, and so it is a big cycle and so you really have to make sure that they are staying ahead of it on fluids. Your urine should look more like lemonade than apple juice is what I always tell my patients. Every time you go to the rest room, it should make you think you got to take a drink, right? You don't want people drinking gallons of water and becoming water toxic because it can happen, but really make sure that they are aware that they need to be hydrated. Then the other thing is make sure there is a lot of good education going on about the antiemetics and whether they need to be scheduled or prophylaxis, or if you know this is the time of the day every day you get sick, take it 20 minutes before that.

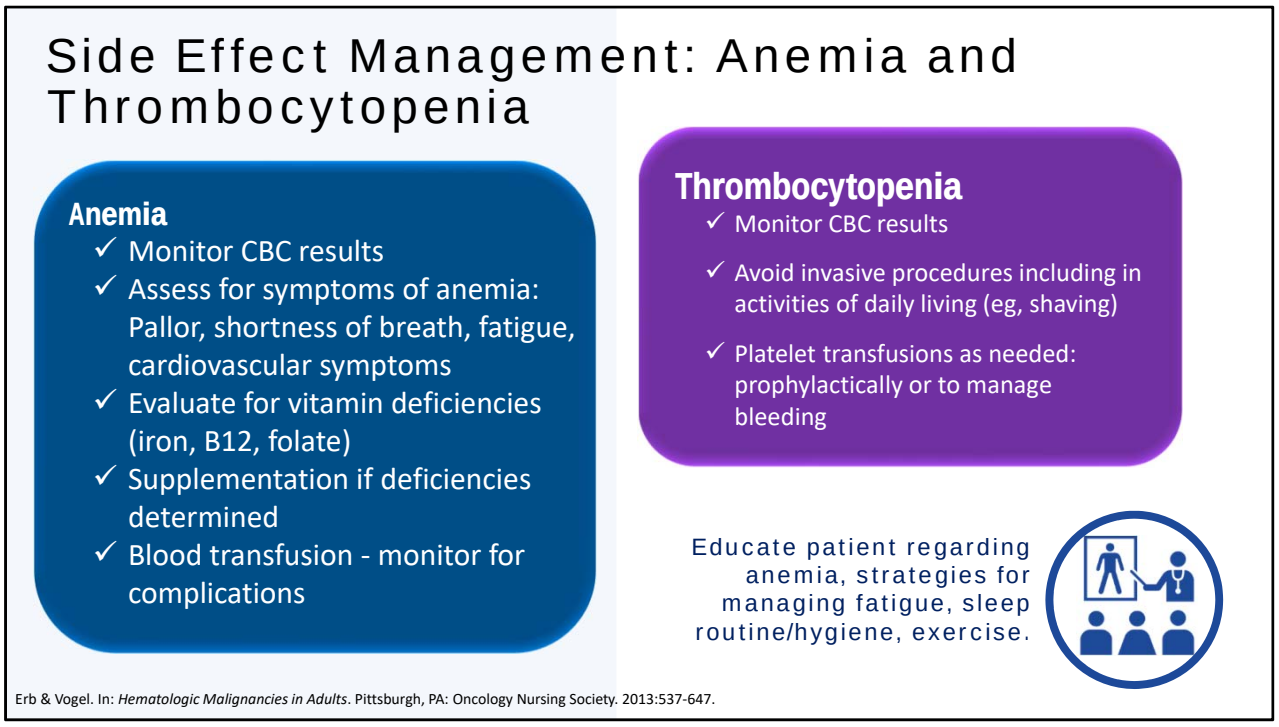
Pulmonary Toxicity

cHL therapies associated with late pulmonary toxicity

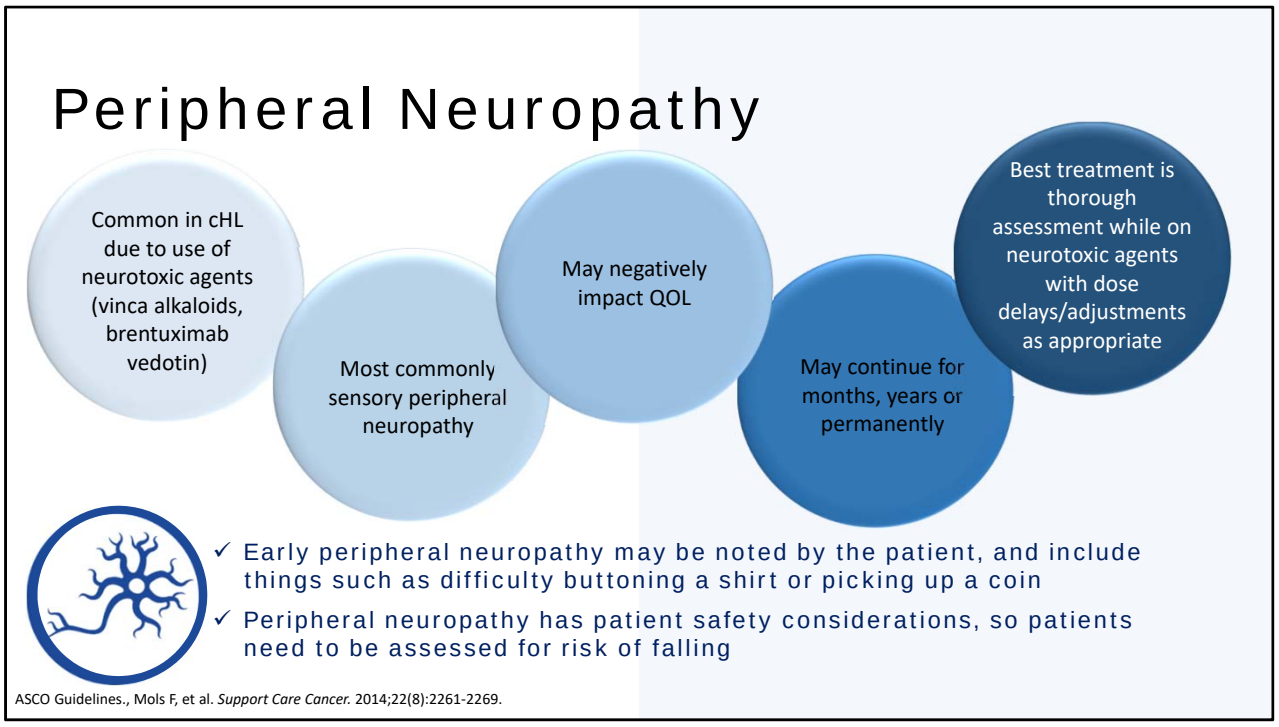
Injury	Drug/Regimen
Interstitial/pulmonary fibrosis	Bleomycin, busulfan, cyclophosphamide, gemcitabine, cytarabine, vincas
Pulmonary vascular disease/pulmonary veno-occlusive disease	Bleomycin, busulfan
Pleural effusion	Busulfan, thoracic radiation
Airway disease • Bronchiolitis obliterans syndrome • Bronchiectasis	• Thoracic radiation, busulfan • Thoracic radiation

ASCO Guidelines, 2018.; Skinner R, et al. *Semin Oncol*. 2013;40:757-773.

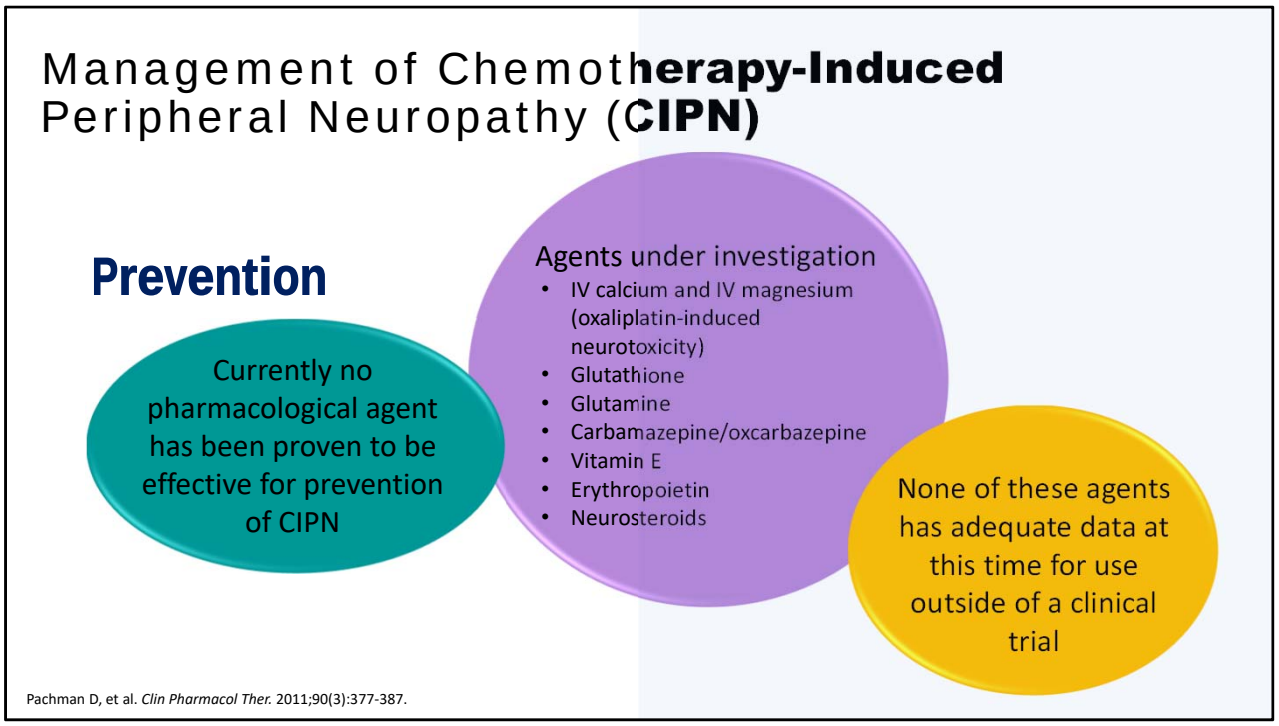
Pulmonary toxicities, Amy touched on these as well with the bleomycin. There are some other drugs that cause pulmonary toxicities as well. Busulfan's, cyclophosphamide, gemcitabine Cytarabine, the vincas. So there are some predisposing factors, pulmonary disease, COPD, emphysema, a lot of these drugs if you have a history of a pulmonary effusion or a pleural effusion, airway disease, someone who has bronchitis and bronchiectasis and all those other kind of things. Always assess patients' lung function before you get started on a regimen for Hodgkin's disease, that is standard of care, everybody gets checked out ahead of time. And then be in tune for subtleties, do not wait until it is a disaster. If they are saying they have shortness of breath and cough and tightness in their chest, do the evaluations, hold the therapy for the day, get to the assessments because a lot of these toxicities can get much worse even with the next dose and have some irreversibility and the consequences can be detrimental.



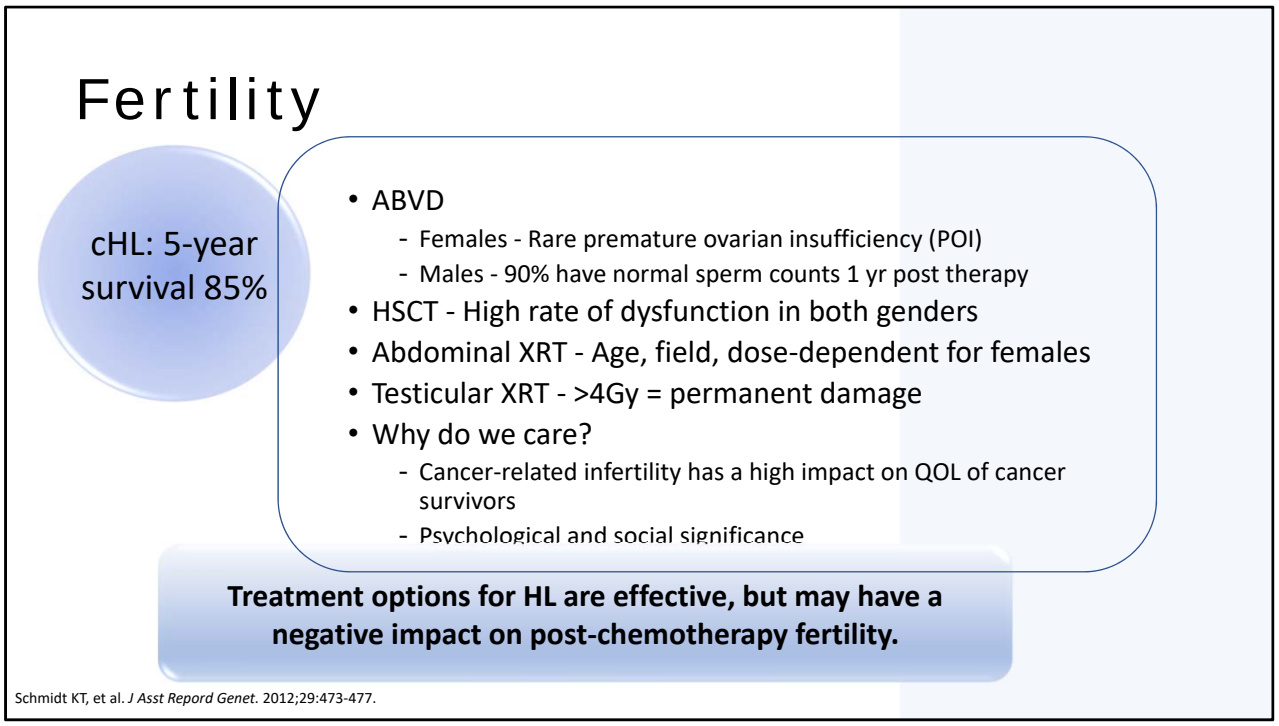
Anemia and thrombocytopenia, again, not new to the game. Monitoring a CBC is one of the best ways you can tell if someone is anemic, you can always look at their eyes and under their tongue and all that other stuff. Symptoms of anemia, we know those, shortness of breath, fatigue, achy legs, cardiovascular symptoms. Always evaluate for additional causes of anemia whether it is dietary, supplements, anything, other drugs, before you go jumping right in and blame the Hodgkin's disease or the treatment for the Hodgkin's disease because they may have other things going on as well because they may have been sick coming into this, and a 65-year-old and above, comorbidities, right? All kinds of other things that can cause these transfusions if necessary. Again, rare in the younger folks with Hodgkin's disease, more common in folks who are on repeated therapies and in relapse. Thrombocytopenia, monitor the CBCs, see what the platelet count is, avoid invasive procedures including activities of daily living like shaving. So if your platelets are low, do not shave your legs. So, anyway, just being preventive medicine, an ounce of prevention.



Platelets counts, platelet transfusions if necessary. Education, education, education. Teach patients. The more they know, the better they are going to be. Peripheral neuropathy is something that we touched on a lot in these regimens because they do have a high incidence of peripheral neuropathy, and peripheral neuropathy can start out as tingling in your finger or toes and it can become devastating in a huge leap in a short period of time, and so, it is important to always ask the questions upfront. Are you having numbness and tingling in your fingers and toes? Are you having trouble picking up change? Can you button your shirt? You can have central neuropathies as well. Some of the constipation and some of the GI distress can be caused by neuropathies that are caused in the central part of, as opposed to peripheral neuropathy, you can have viscera neuropathy as well, and it can improve over time but it can last for months, years, and possibly never go away when you are done. That is the hardest thing to tell patients is that when they say is this going to get better when I am done with the treatment? You know you have your fingers crossed and you hope so, so the best thing is to cut it down, nip it in the bud. I may goof around about stuff, but ask the questions, find out upfront. If you do not ask them, they may not know to report it as a symptom, right? And so I have seen patients who have just come out of the chemotherapy suite and whether someone had not assess them or did not ask the questions and they report to me that they have been fine, and then I see them walking down the hallway and they are walking like they have ski boots on, that should have rung a bell to someone, but if you did not see them, falling, all those kind of things.



How do you manage chemotherapy-induced peripheral neuropathy prevention? We do not have any current pharmacologic medicines that help it get better and that prevent it. There are lot of agents under investigation. IV calcium, IV magnesium, oxaliplatin, in some of the solid tumors they look those things, glutamine, vitamin E, erythropoietin, neuro-steroids, but none of them have adequate data to say that they are going to reduce peripheral neuropathy and so, prevention is the best thing that we can do.



Fertility, Amy touched on this as well. This is an issue in Hodgkin's disease, certainly in the younger group. Again, a peak of about 19, 20 years old just starting to think about families and marriage or maybe not even at that point in their life, we always offer fertility counseling in the younger population, whether it is male or female, prior to ABVD. Sometimes you have a little wiggle room there. Sometimes you do not, but females, it is rare that they would have premature ovarian insufficiency or POI with ABVD. Males have about 90% of sperm count. There are two ways that you find out about fertility in young men in Hodgkin's disease. They call your office and they say, "I thought you told me I was going to be sterile with chemotherapy?" No, never said that. Let me guess. We have all had the call, we have all taken the call. and the other one is that they want to and they have to go to the doctor.

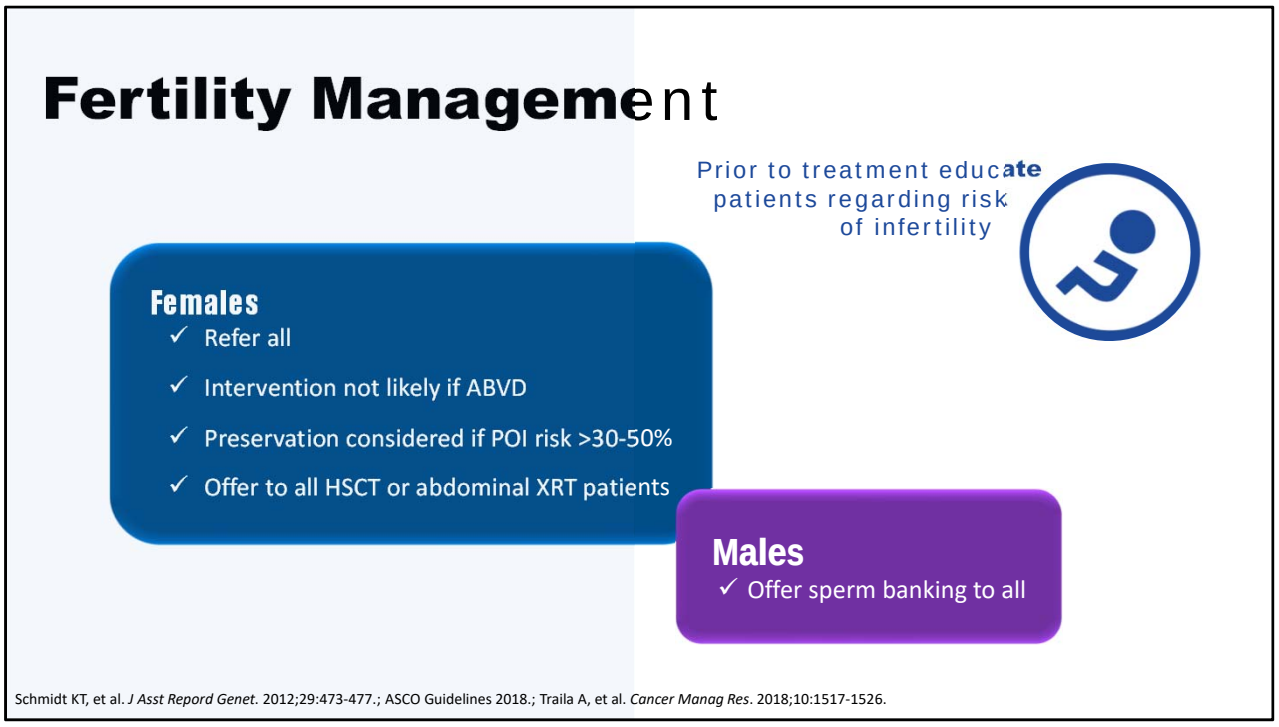
Fertility Options

Female options	Male options
Co-treatment with Gonadotropin Releasing Hormone agonist (easy, inexpensive, trials show inconsistent results)	Spermatozoa cryopreservation (well-established, quick, easy, success rates 33-56%, offer to all, regardless of risk of testicular failure, malignancy can impact sperm quality)
Oocyte cryopreservation (aspirated in connection with IVF, live birth rate 21-38%)	Transrectal electro-ejaculation in young pubertal boys (possible future option for pre-pubertal boys)
Embryo cryopreservation (IVF-induced embryos, requires at least one menstrual cycle, live birth rate 21-38%)	
Ovarian tissue cryopreservation (entire or part of ovary preserved, quick, often first choice, only option for pre-pubertal girls, may need laparoscopy, autotransplant of tissue in 3-4 yrs can restore menses and hormone production, 20+ live births)	
In vitro maturation of oocytes (quick, high rate of early pregnancy loss)	

Schmidt KT, et al. *J Asst Repord Genet*. 2012;29:473-477.

Stem cell transplant, if they are going to have abdominal radiation therapy, if they are going to have testicular radiation therapy, and it may not be an issue now, but 30 years down the road if they had not done something or had not been proactive, it can certainly affect their quality of life, but we want to make sure that those options are given. You do not want to delay treatment any more than you have to, but as Amy pointed out, at five years, 85% of these folks are still around without evidence of disease and what we kind of lean towards the cure, and you hate to have them miss opportunity to have done something preventatively.

There is all options, it used to just be sperm banking and then the other option was to give high dose birth control pills to protect the ovaries, but now ovaries can be frozen--not your whole ovary, eggs, right? Eggs could be frozen without being fertilized, they can be harvested and frozen, you can do embryos, you can do all kinds of things, and so making those opportunities available to this population is important.



We refer all females, again, it is not likely to cause a problem with ABVD, we have many, many patients that we see in long-term follow up where you see their beautiful, healthy, normal babies, and even folks who get pregnant while they are getting chemotherapy, not something we recommend but something we deal with, and then if their risk factors are higher than 30% to 40% of not having preservation, and then anybody who is going to have radiation therapy to their pelvis or stem cell transplant, and then sperm banking for all males, we offer it.

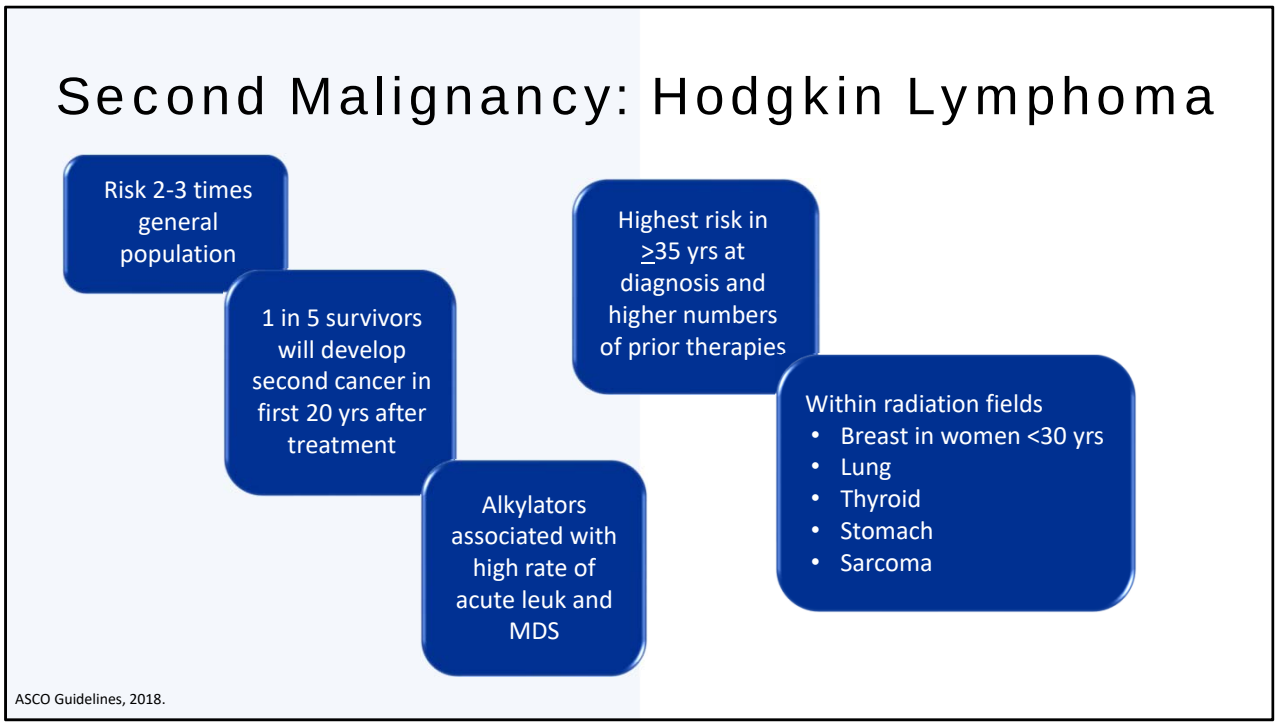
Late and Long Term Toxicities

Toxicity	Contributing factors	Prevention strategies	Treatment
Cardiotoxicity (LV dysfunction, CHF, stroke, MI) May occur during, shortly after or years after treatment, often irreversible	Anthracyclines (bolus, 450-550 mg/m^2) #2 cause of M&M at 5+ years Chest radiation	Consider less toxic agents/liposomals Consider late EF monitoring	Follow guidelines (ACE inhibitors, B-blockers, BP and P control, fluid and salt limits, other agents as appropriate)
Renal Toxicity (glomerular and tubular damage) Subclinical evidence in 20%, may progress to acute or chronic failure	Mainly salvage regimens (ifosfamide, platinums, HSCT) Immunosuppressive agents Anti-infectives Comorbidities	Protective agents not effective in prevention	Avoid polypharmacy Monitor CMP Monitor creatinine clearance Dose reduce appropriate drugs
Fatigue (up to 67% of cHL survivors)	Higher in older patients No correlation with gender, stage or treatment modality	Encourage physical activity	Evaluate disease, other medical causes, depression, psychosocial, pharmacologic. Refer as appropriate

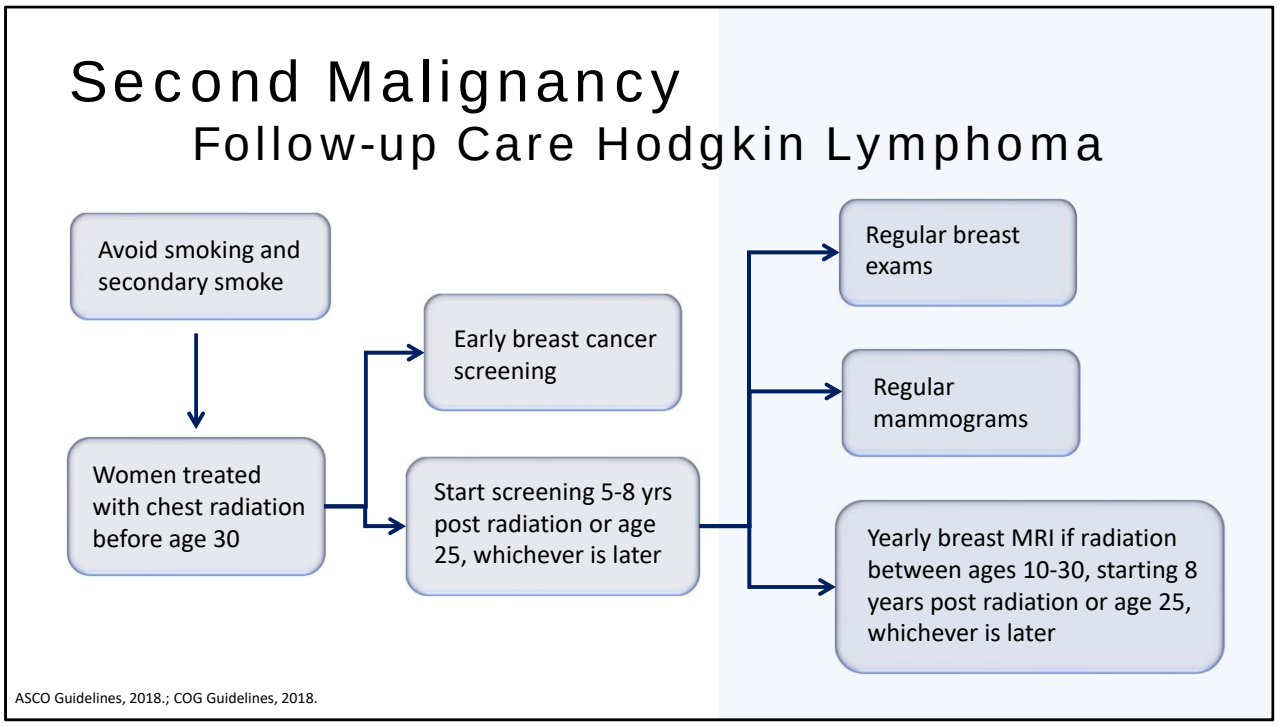
Liminari S, et al. *Hematol Rep*. 2011:3(s3):e4.; Eschenhagen T, et al. *Eur J Ht Failure*. 2011:13,1-10.; Dafts BC, et al *JACC Cardiovasc Imaging*. 2013;6(8):877-885.; Schlitt A, et al. *Dtsch Arztebl Int*. 2014;111:161-168.; Skinner R, et al. *Semin Oncol*. 2013:40,757-773.; Vermaete N, et al. *Ann Hematol*. 2012;92:1007-1021.; Daniels LA, et al. *Ann Hematol*. 2013:92:1023-1032.; ASCO Guidelines, 2018 .

Late term toxicities. Young group of people getting some heavy doses of chemotherapy and potential radiation therapy at an early stage in their lives when tissues are developing and continue to grow. There are cardiotoxicities that can come from the anthracyclines, you have to think about lifetime dosing of anthracyclines, you are not going to hit it with ABVD but it is a possibility, it is something you have got to think about. Sometimes the liposomal treatments are better and somebody who may have already had another disease and is now requiring treatment for ABVD, we have seen a bit of a tick in the up rise, not huge but some transformations in the last few years of CLL to Hodgkin's disease, and so those folks come with a whole another toxic can of worms there. Renal toxicity. The other thing that can contribute to cardiac toxicity is radiation to your chest, right? So mediastinal mass is common in these patients at presentation, and so you want to sort of think long-term about preservation of tissue, whether it is avoiding the heart area or avoiding the breast tissue. They try to do as minimal field involvement as they can for Hodgkin's radiation therapy, and now that you do 2 cycles of ABVD and then involved field radiation in a low risk patient, you have got to think about these long-term ramifications as well.

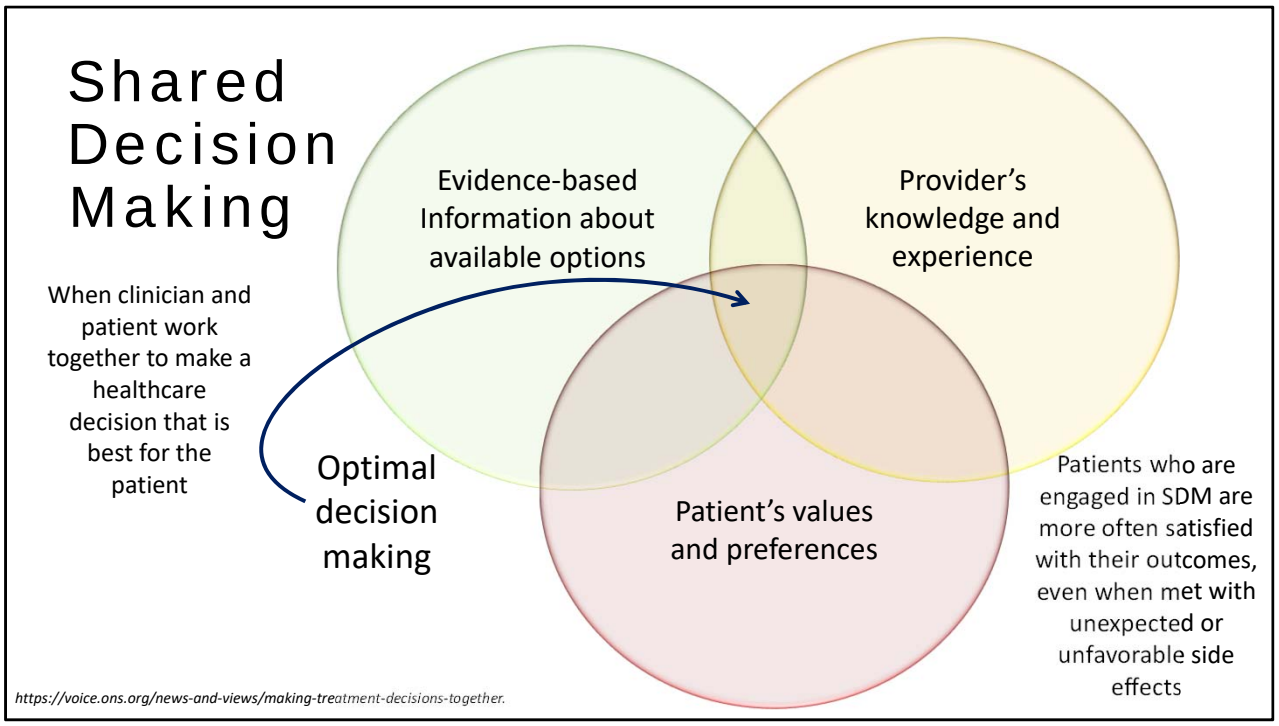
Renal toxicity and glomerular and tubular damage, usually in the salvage regimen, so we are kind of kicking people who are already down. There are not any great protective agents, and you want to avoid polypharmacy, things that are dinging the kidneys as you are going along, fatigue, always a complaint, always a problem. Cancer treatment and cancer in general is higher in older patients. There is no gender, everybody gets it. Encourage increased physical activity and we know a lot of those things, rule out all the organic causes but we know as nurses, the kind of things that we are supposed to recommend or that we do recommend for the treatment of cancer fatigue.



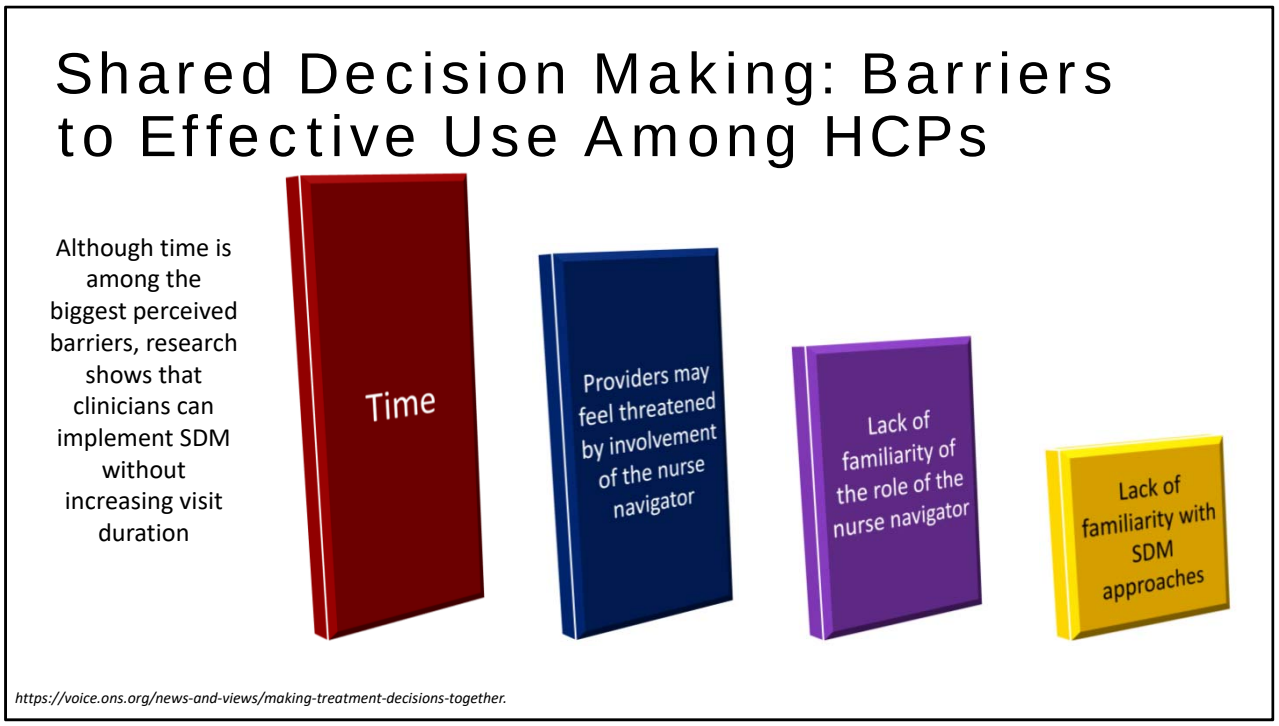
There are secondary malignancies in Hodgkin's lymphoma. The risk is two to three times higher than the general population. So once you have had a hemalignancy, you have a higher risk of developing a secondary one. Myelodysplastic syndrome is high. There is a higher rate of leukemia and this is because you have exposed their bone marrow or the manufacturing center to either radiation or a lot of toxic soup and so you have got this already destroying a baseline here. The highest risk in greater than 35 years at diagnosis, and the number of prior treatments, so the older you are, the more treatments you have had, that puts you at higher risk. Then again, we talked about within the radiation fields, so lung thyroid, a lot folks have thyroid dysfunction after treatment with ABVD and involved field radiation and so this is something we monitor very closely and we work with the endocrinologist to make sure that there is not some other things that we need to do.



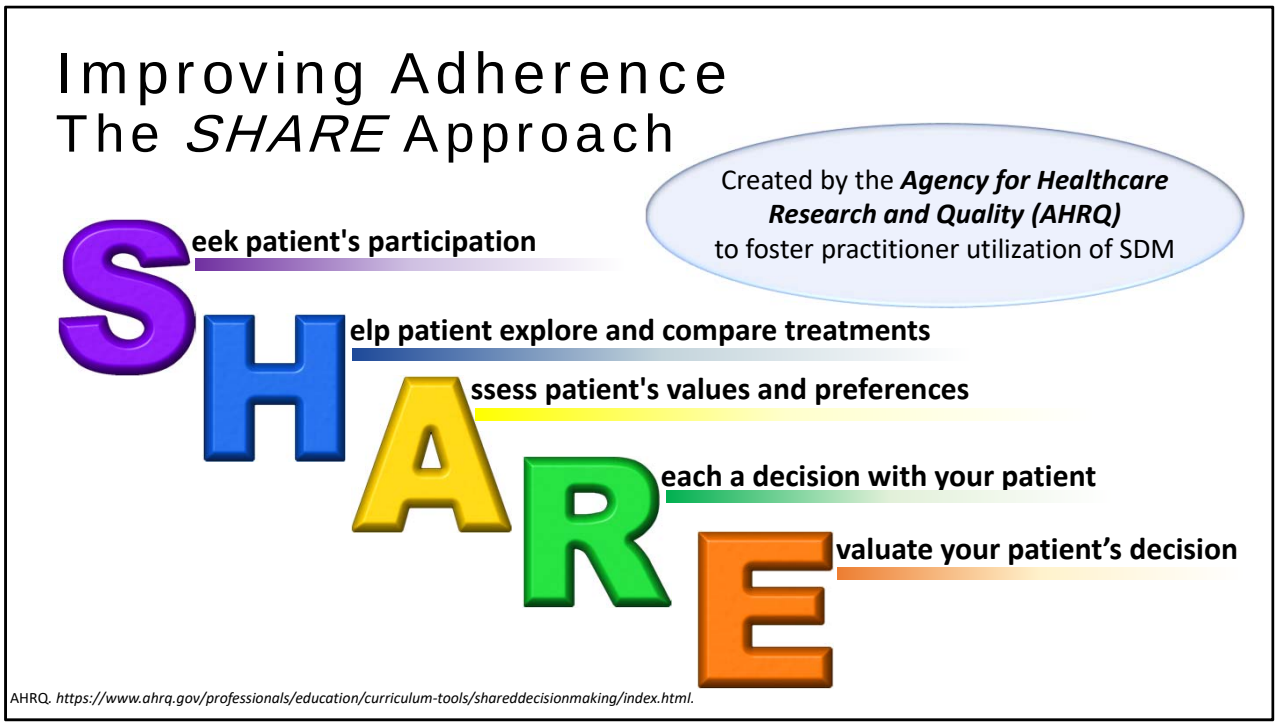
We recommend that Hodgkin's disease patients do not smoke, do not start smoking just because you had a cancer you're not exempt from getting another one so do not start, and avoid secondary smoke, chest radiation before 30, early breast exams, starting screening, five to eight years post radiation or the age of 25, whichever comes first. So if you are close to that, at age 25, but if you are much younger when you were diagnosed, you start at age 25, breast exams, mammograms, MRIs, and close observation.



So now, shared decision making. This is the last part of this program that we talked about, so that was the management of the treatment side effects and how do we help folks with that. Shared decision making is something that you have probably been hearing more and more about and it is the way that we as providers can involve patients and families and caregivers and the whole team in the process of making decisions as a group so that the patient can be better treated, feel like they are more part of the decision process, better compliance, all of those things thrown in together. The best way to make decisions is if you do have input from both the patient, the providers, the family, the team, and so you can do it. Gone are those days where people walk in and say whatever the doctors says, we have got a bit more of a savvy group of patients now. So it includes their preferences and their religious beliefs and sort of puts the whole patient in it together. It is tricky in the beginning of a diagnosis of Hodgkin's disease because what has to happen is you get treatment for Hodgkin's lymphoma. It is a curative disease, you are going in with curative intent. It is important that you get started and that you stay on the regimen, so the decision making process about treatment, actual chemo treatment, is going to be a little bit more driven by the science and the care-providing team. It is all of those other decisions that come in along with it that may be more suitable to a decision making process that it shared. How can we help you feel better? Tell me about your symptoms. What, what barriers are keeping you from coming to clinic? What barriers are keeping you from getting your medicines? So those kind of shared decisions may be a bit easier to do, and then certainly in the relapse setting, when you are trying to decide which part of the arm of the tree you go down, but in the upfront part, it may be a little trickier because you have got to get going on therapy.



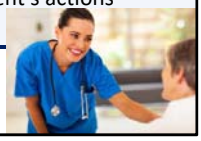
So, what kind of things are barrier? Time? We do not have time. You are doing 50 things, you got 10 patients in chairs, you got a pager going off, you are making phone calls, you are waiting for the pharmacy to deliver medicine that you ordered 10 hours ago, I mean, just everything. The nurse navigators are a big part of that and the patients, and sometimes, physicians feel that they might be losing a little bit of their control over it. The nurse navigator role may not be well known and some people, some practices and some physicians and providers, not just physicians, providers in general, as well as family members may not be aware of the options to do for shared decision making.



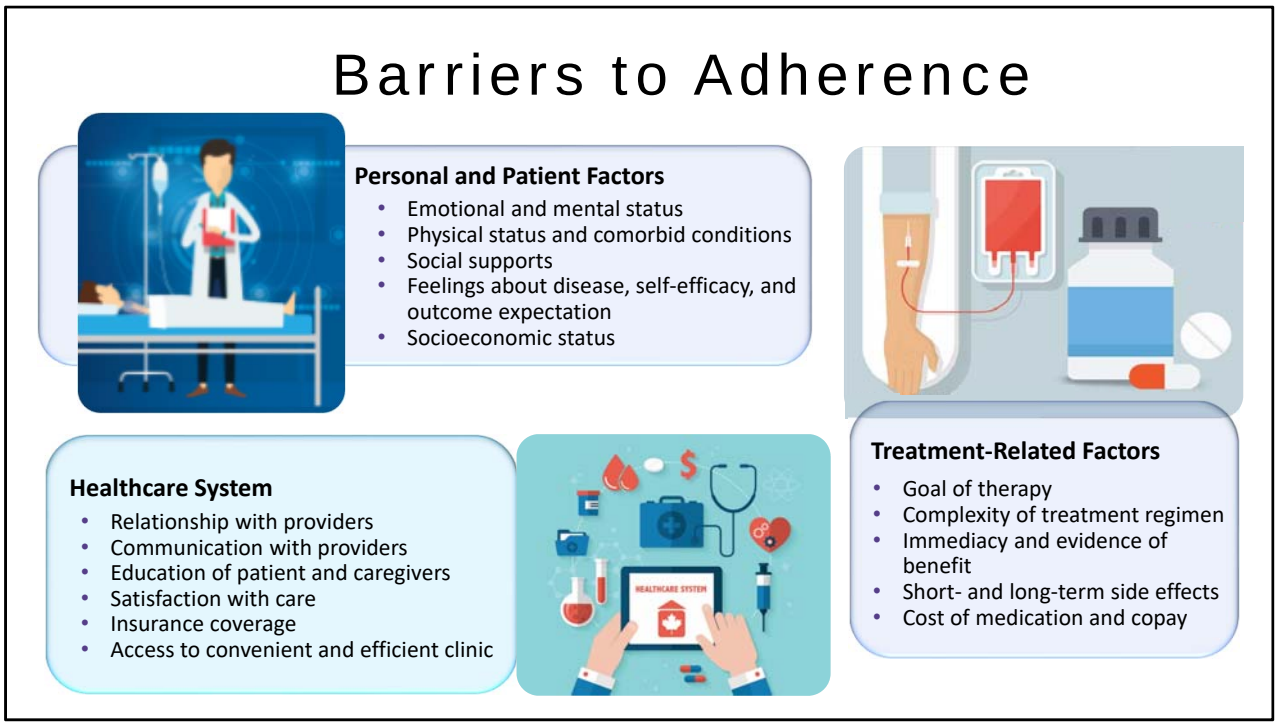
So how do we improve adherence with the shared approach? Well, ask the patient to participate. Help them explore and compare treatments. This is what we are going to do, if you do this, A, B and C could happen. If you do number 2, then D, E and F can happen. If you do not do anything… so they are aware of what they are, as consumers, what they are consuming. Again, asses their values, reach a decision with your patient. Again, it may not be feasible with actual frontline therapy in Hodgkin's disease but there are a lot of other things that you can fit in to this model, and then help them evaluate. Did they make the right decision? Does it still fit with what they believe? Did they learn more as they go along? Because at first they just hear that word cancer, lymphoma, is this the good lymphoma, right? Because one is good and one is bad. Hodgkin's versus non-Hodgkin's, which is the good one? Neither. Nobody lives longer because they have been diagnosed with a lymphoma. I will tell you that. Neither.

Improving Adherence Communications Approaches

Traditional Counseling		Motivational Interviewing
• HCP is the healthcare expert • Assumes patient lacks knowledge • Tells patient what to do • Hopes patient follows instructions	→	• HCP develops partnership with patient • Exchanges information to facilitate an informed decision • Patient has the right to decide own care
• HCP provides definitive information • Directives are presumed to be non-negotiable	→	• HCP provides information to patient for the purpose of developing discrepancy between present behavior and goal
• HCP dictates healthcare behavior	→	• HCP and patient negotiate behavior and reach agreement
• Goal is to motivate the patient	→	• Goal is to access motivation and elicit patient's commitment to change behavior
• HCP persuades patient to change behavior	→	• HCP understands and accepts patient's actions
• HCP expects respect from patient	→	• HCP must earn respect from patient



How do we improve adherence? Things that we do on a very regular basis with a healthcare provider, has the expert knowledge, how do we motivate people to do it? Partner with the patients, ask their opinion. Disseminate information as best you can. Are they understanding it? Are they comprehending it? Getting their feedback. There are some things that are not negotiable. There are some things that are absolutely negotiable in cancer treatment on any level, and then come to an agreement with the patient. Sometimes, my decision is not their decision. I had a kid tell me yesterday who is noncompliant with his visits in a relapsed Hodgkin's disease setting for whatever reasons, and I said we really need you to sort of work on sticking to the plan here and he said, you know what, life gets in the way and it is not a life that I planned. And I thought, ah, you are right, my plan and my layout contract here is a little bit different than yours and sometimes mine does not work, and so we are trying to come up with ways to help him feel like he has got some more control of things and so that he can have improvement.



There may be personal factors, whether they are too emotional or too upset, or there may be mental health issues that need to be dealt with on a start. Physical status, are they too sick to make a decision? So you have to sort of weigh in on all of those kind of things. Is it the healthcare system? Are there not enough providers? Do they not know how to get into the system? Do they not know what services are available through the system and sort of helping them to navigate around that. This is where nurse navigators, hence the word, nurse navigator, can help them get through those. Are the drugs too expensive? Do they know where to pick them up? Do they know how to get supplements? Do they know how to help pay for some of these things? Can you navigate your insurance? Are you losing your insurance? All those things together, healthcare has become so much more complicated and then we need so many more hands helping to sort of sort people and guide people through. It is important that we take advantage of these as healthcare providers.

SUMMARY

Oncology nurses are in a critical position to assure prevention, identification and prompt management of side effects to optimize short term and long term outcomes

- cHL treatment side effects are expected and potentially severe
- Long term and late treatment related side effects are common in cHL survivors
- Diligent management before, during and after treatment may lessen side effects during treatment and also late and long term effects
- Patient education is critical, as it fosters shared decision making

Good communication among all providers is key

During all phases of care, focused assessments, exams and screening as appropriate

Oncology nurses are in a very critical position to assure prevention, identification, promote management of side effects, and optimize short-term and long-term outcome. As oncology nurses, we are the frontline of what is going on, what is happening with the patient. Subtleties and changes can make a big change in long-term adherence, compliance, long-term side effects, long-term damages. Classical Hodgkin's treatment side effects are expected and potentially severe so be aware of them. Long-term and late treatment related side effects can happen. Be aware of what to look for when you are sending your patients back to the community, make sure you communicate in the care plan or survivorship plan what is expected. These are the potential side effects that we are looking for in the long-term. Here is when you do your monitoring, here is what you do for monitoring. Manage them before, during, and after treatment. Again, this is a cyclic therapy. They are coming in all the time and all of a sudden they are not, they start spacing out their visits, so you have to make sure that they are reporting late and long-term side effects to you as well. Education, education, education, wash your hands, wash your hands, wash your hands, wash your hands, education, education, and be focused in your exams and assessments and report accordingly.