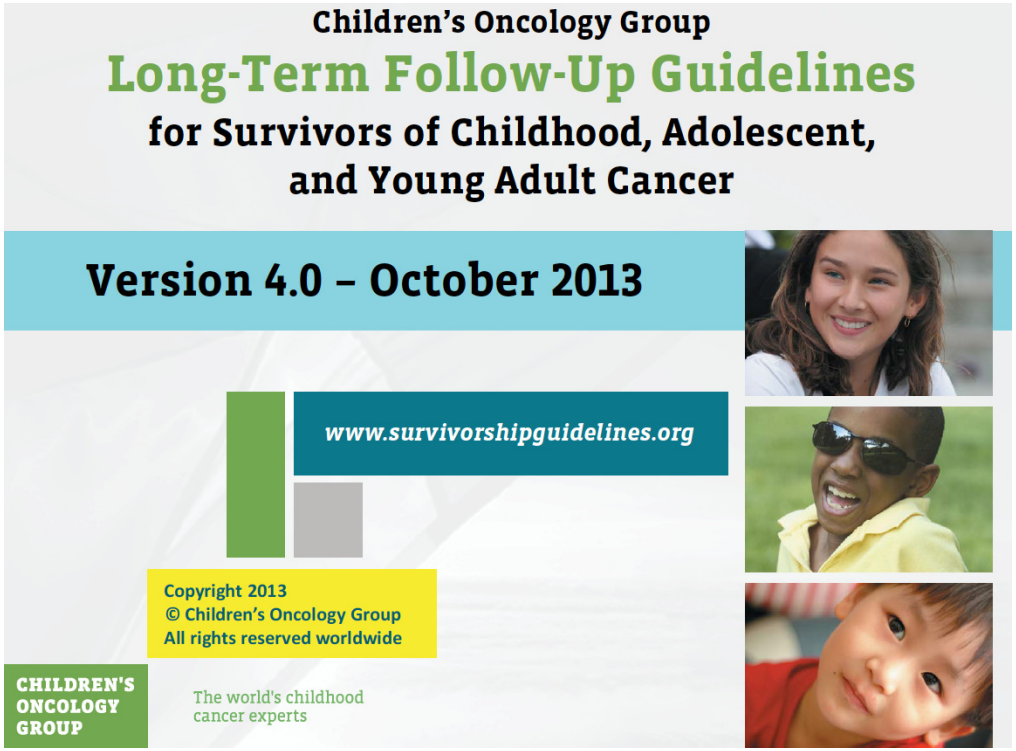
Children's Oncology Group Long-Term Follow-Up Guidelines for Survivors of Childhood, Adolescent, and Young Adult Cancers



Matt Ehrhardt, MD, MS

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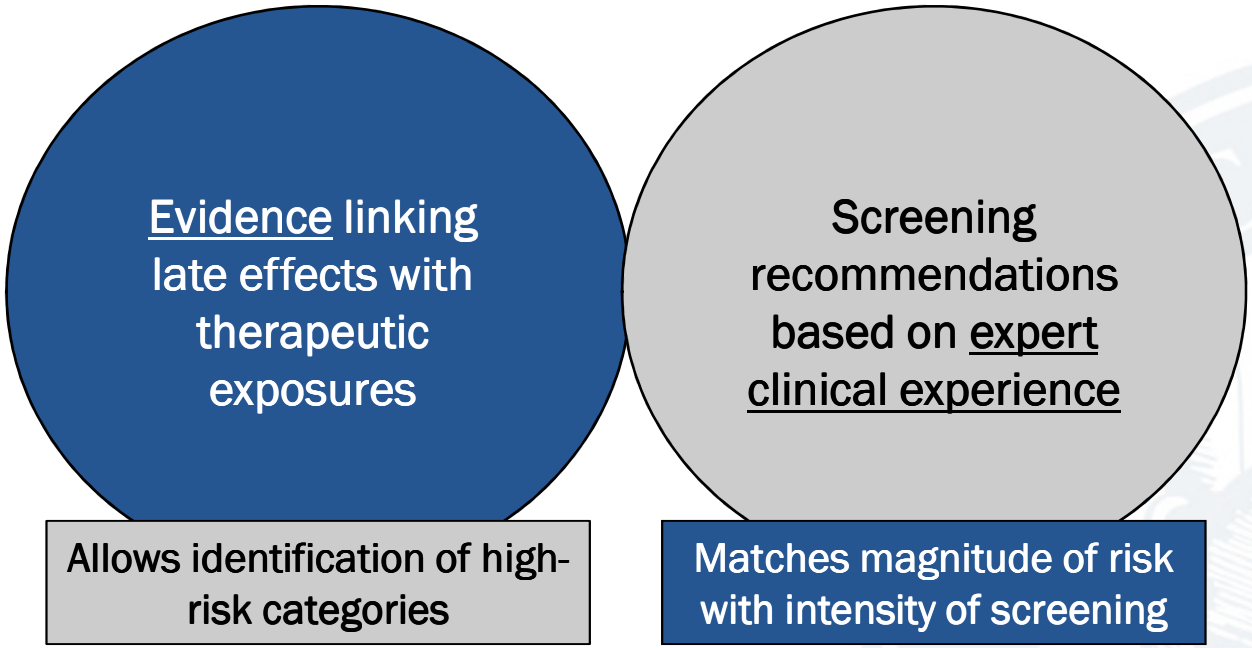
Evidence-Based Guidelines for Childhood Cancer Survivors: A Hybrid Model



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National Comprehensive Cancer Network "Categories of Consensus"

- **Category 1** – Uniform consensus of the panel that: (1) there is high-level evidence linking the late effect with the therapeutic exposure and (2) the screening recommendation is appropriate based on the collective clinical experience of panel members
- **Category 2A** - Uniform consensus of the panel that: (1) there is lower level evidence linking the late effect with the therapeutic exposure and (2) the screening recommendation is appropriate based on the collective clinical experience of panel members
- **Category 2B** – Non-uniform consensus of the panel that: (1) there is lower level evidence linking the late effect with the therapeutic exposure and (2) the screening recommendation is appropriate based on the collective clinical experience of panel members
- **Category 3** – There is major disagreement that the recommendation is appropriate

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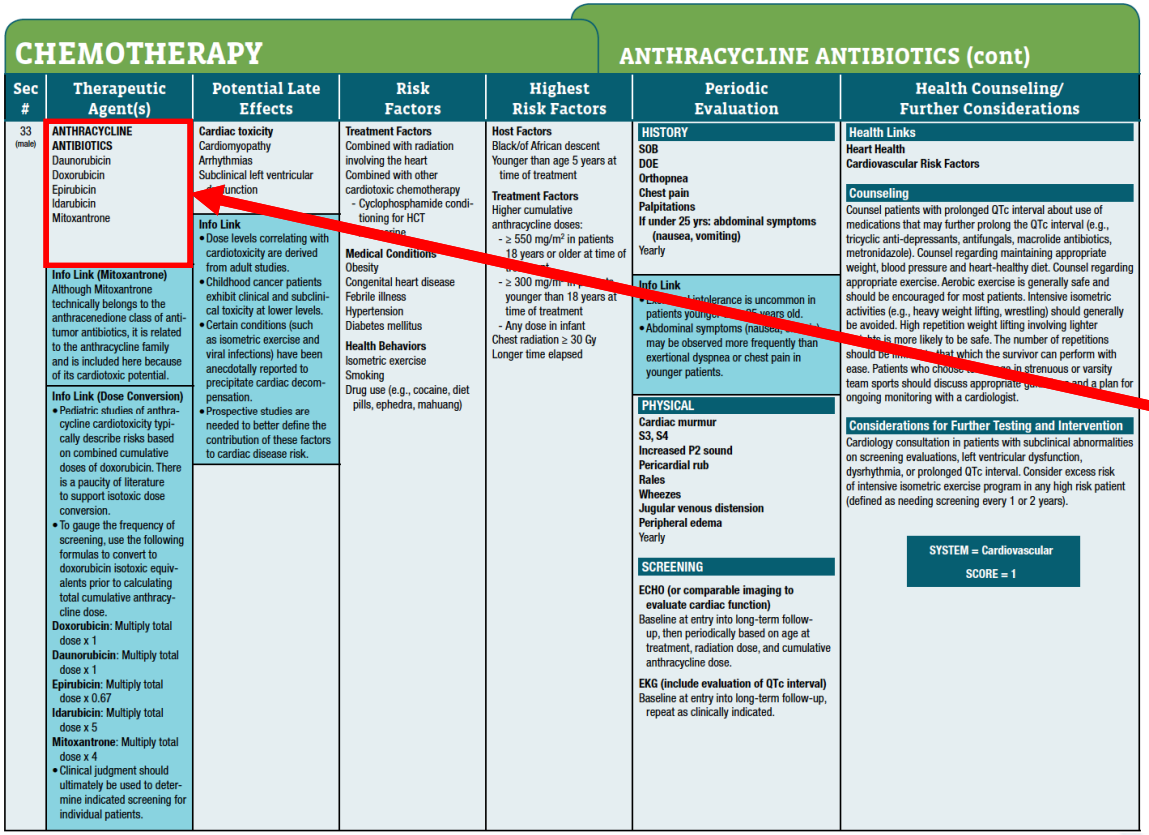
COG Guideline Example



CHEMOTHERAPY — **ANTHRACYCLINE ANTIBIOTICS (cont)**

Sec #	Therapeutic Agent(s)	Potential Late Effects	Risk Factors	Highest Risk Factors	Periodic Evaluation	Health Counseling/ Further Considerations
33 (male)	**ANTHRACYCLINE ANTIBIOTICS** Daunorubicin Doxorubicin Epirubicin Idarubicin Mitoxantrone **Info Link (Mitoxantrone)** Although Mitoxantrone technically belongs to the anthracenedione class of anti-tumor antibiotics, it is related to the anthracycline family and is included here because of its cardiotoxic potential. **Info Link (Dose Conversion)** • Pediatric studies of anthracycline cardiotoxicity typically describe risks based on combined cumulative doses of doxorubicin. There is a paucity of literature to support isotoxic dose conversion. • To gauge the frequency of screening, use the following formulas to convert to doxorubicin isotoxic equivalents prior to calculating total cumulative anthracycline dose. **Doxorubicin**: Multiply total dose x 1 **Daunorubicin**: Multiply total dose x 1 **Epirubicin**: Multiply total dose x 0.67 **Idarubicin**: Multiply total dose x 5 **Mitoxantrone**: Multiply total dose x 4 • Clinical judgment should ultimately be used to determine indicated screening for individual patients.	**Cardiac toxicity** Cardiomyopathy Arrhythmias Subclinical left ventricular dysfunction **Info Link** • Dose levels correlating with cardiotoxicity are derived from adult studies. • Childhood cancer patients exhibit clinical and subclinical toxicity at lower levels. • Certain conditions (such as isometric exercise and viral infections) have been anecdotally reported to precipitate cardiac decompensation. • Prospective studies are needed to better define the contribution of these factors to cardiac disease risk.	**Treatment Factors** Combined with radiation involving the heart Combined with other cardiotoxic chemotherapy - Cyclophosphamide conditioning for HCT - [illegible] **Medical Conditions** Obesity Congenital heart disease Febrile illness Hypertension Diabetes mellitus **Health Behaviors** Isometric exercise Smoking Drug use (e.g., cocaine, diet pills, ephedra, mahuang)	**Host Factors** Black/of African descent Younger than age 5 years at time of treatment **Treatment Factors** Higher cumulative anthracycline doses: - ≥ 550 mg/m² in patients 18 years or older at time of [illegible] - ≥ 300 mg/m² [illegible] younger than 18 years at time of treatment - Any dose in infant Chest radiation ≥ 30 Gy Longer time elapsed	**HISTORY** **SOB** **DOE** **Orthopnea** **Chest pain** **Palpitations** **If under 25 yrs: abdominal symptoms (nausea, vomiting)** Yearly **Info Link** • [illegible] intolerance is uncommon in patients younger [illegible] 25 years old. • Abdominal symptoms (nausea, [illegible]) may be observed more frequently than exertional dyspnea or chest pain in younger patients. **PHYSICAL** **Cardiac murmur** **S3, S4** **Increased P2 sound** **Pericardial rub** **Rales** **Wheezes** **Jugular venous distension** **Peripheral edema** Yearly **SCREENING** **ECHO (or comparable imaging to evaluate cardiac function)** Baseline at entry into long-term follow-up, then periodically based on age at treatment, radiation dose, and cumulative anthracycline dose. **EKG (include evaluation of QTc interval)** Baseline at entry into long-term follow-up, repeat as clinically indicated.	**Health Links** **Heart Health** **Cardiovascular Risk Factors** **Counseling** Counsel patients with prolonged QTc interval about use of medications that may further prolong the QTc interval (e.g., tricyclic anti-depressants, antifungals, macrolide antibiotics, metronidazole). Counsel regarding maintaining appropriate weight, blood pressure and heart-healthy diet. Counsel regarding appropriate exercise. Aerobic exercise is generally safe and should be encouraged for most patients. Intensive isometric activities (e.g., heavy weight lifting, wrestling) should generally be avoided. High repetition weight lifting involving lighter [illegible]ts is more likely to be safe. The number of repetitions should be [illegible] that which the survivor can perform with ease. Patients who choose [illegible]se in strenuous or varsity team sports should discuss appropriate [illegible] and a plan for ongoing monitoring with a cardiologist. **Considerations for Further Testing and Intervention** Cardiology consultation in patients with subclinical abnormalities on screening evaluations, left ventricular dysfunction, dysrhythmia, or prolonged QTc interval. Consider excess risk of intensive isometric exercise program in any high risk patient (defined as needing screening every 1 or 2 years). **SYSTEM = Cardiovascular** **SCORE = 1**

- Organized around risk-based exposure and appropriate follow-up care
- Exposure specific sections can be found, with corresponding agents listed

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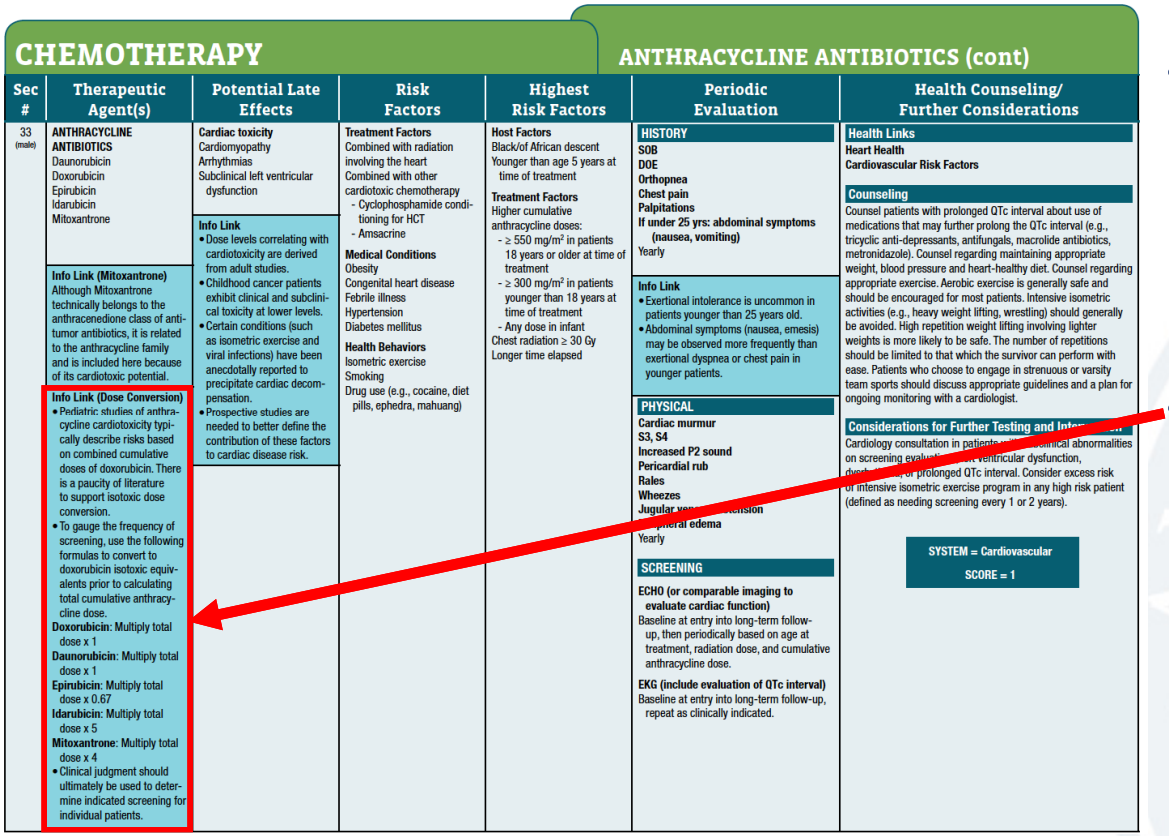
COG Guideline Example



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- "Info Links" are interspersed to clarify components of individual sections
- E.g., anthracycline conversion ratios are including in the anthracycline associated toxicity section

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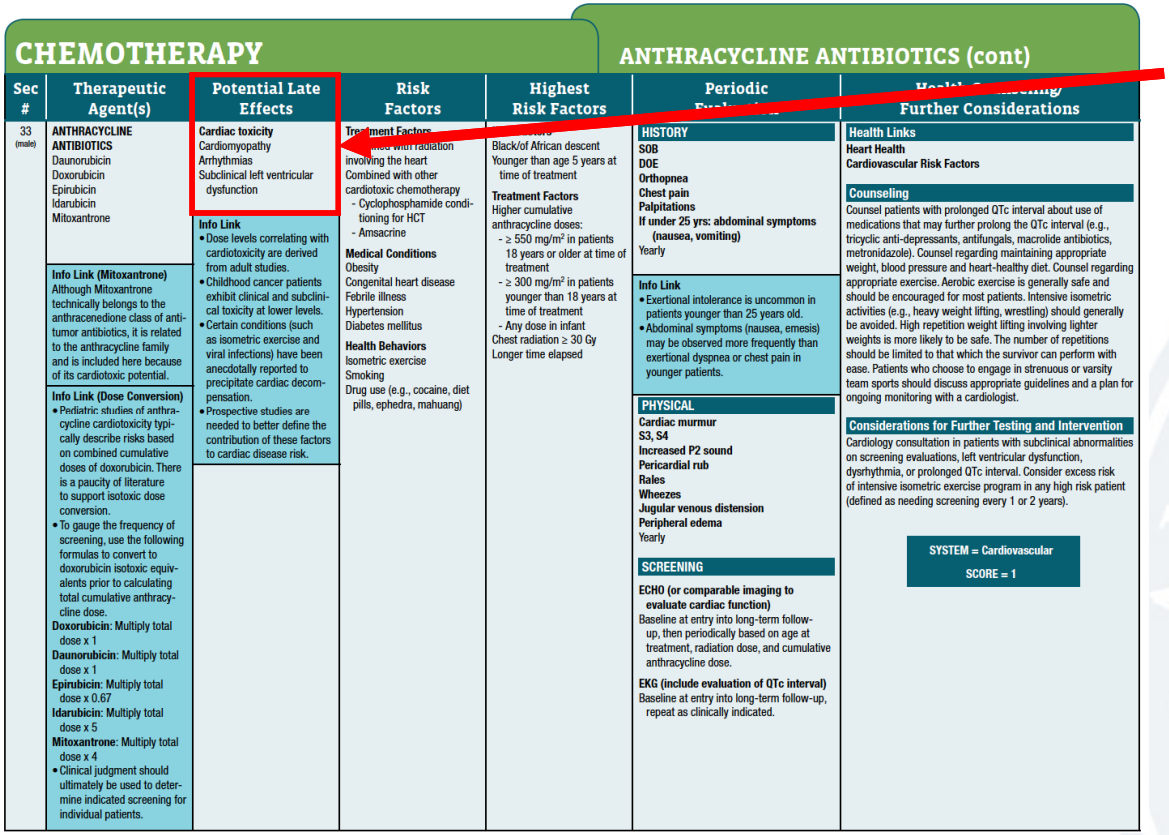

CHEMOTHERAPY | **ANTHRACYCLINE ANTIBIOTICS (cont)**

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Info Link
- Dose levels correlating with cardiotoxicity are derived from adult studies.
- Childhood cancer patients exhibit clinical and subclinical toxicity at lower levels.
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Info Link (Mitoxantrone)
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- Pediatric studies of anthracycline cardiotoxicity typically describe risks based on combined cumulative doses of doxorubicin. There is a paucity of literature to support isotoxic dose conversion.
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Idarubicin: Multiply total dose x 5
Mitoxantrone: Multiply total dose x 4
- Clinical judgment should ultimately be used to determine indicated screening for individual patients.

Info Link
- Exertional intolerance is uncommon in patients younger than 25 years old.
- Abdominal symptoms (nausea, emesis) may be observed more frequently than exertional dyspnea or chest pain in younger patients.

- Pertinent late effects are individually listed

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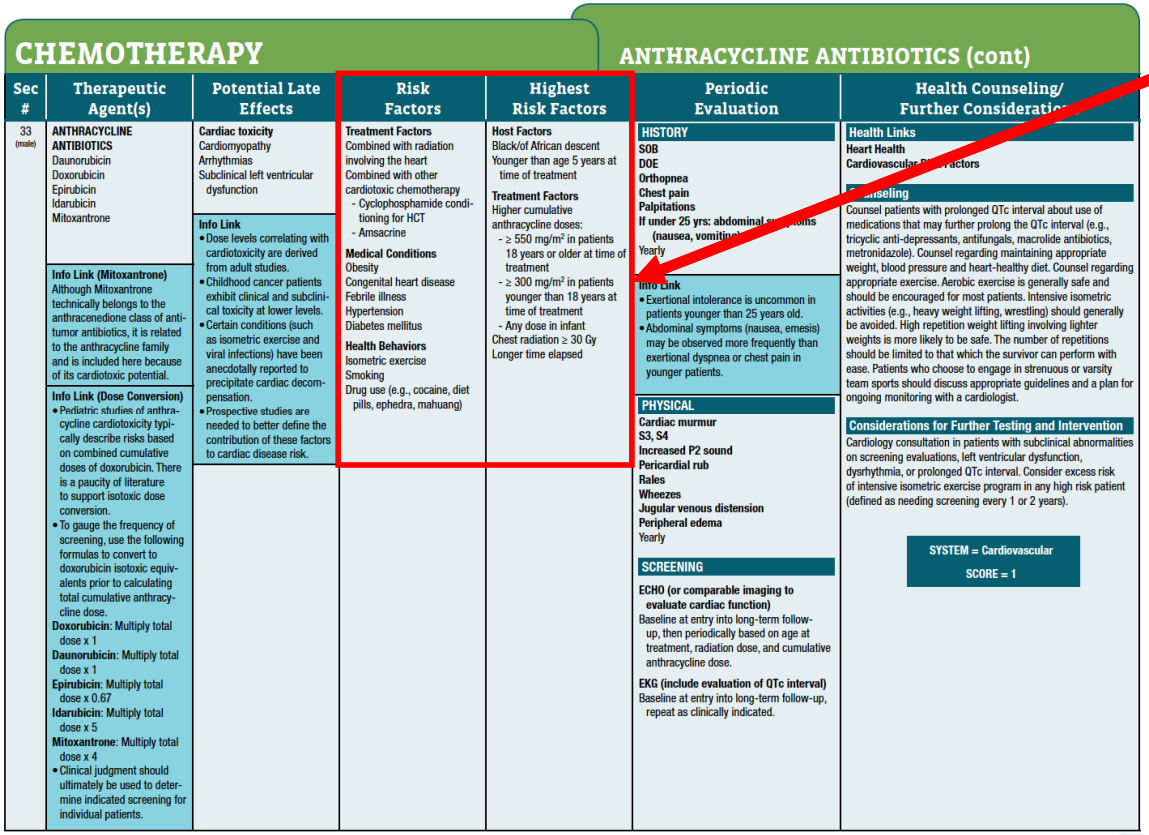

CHEMOTHERAPY

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- Individual risk factors are listed, stratified by increasing degree of risk

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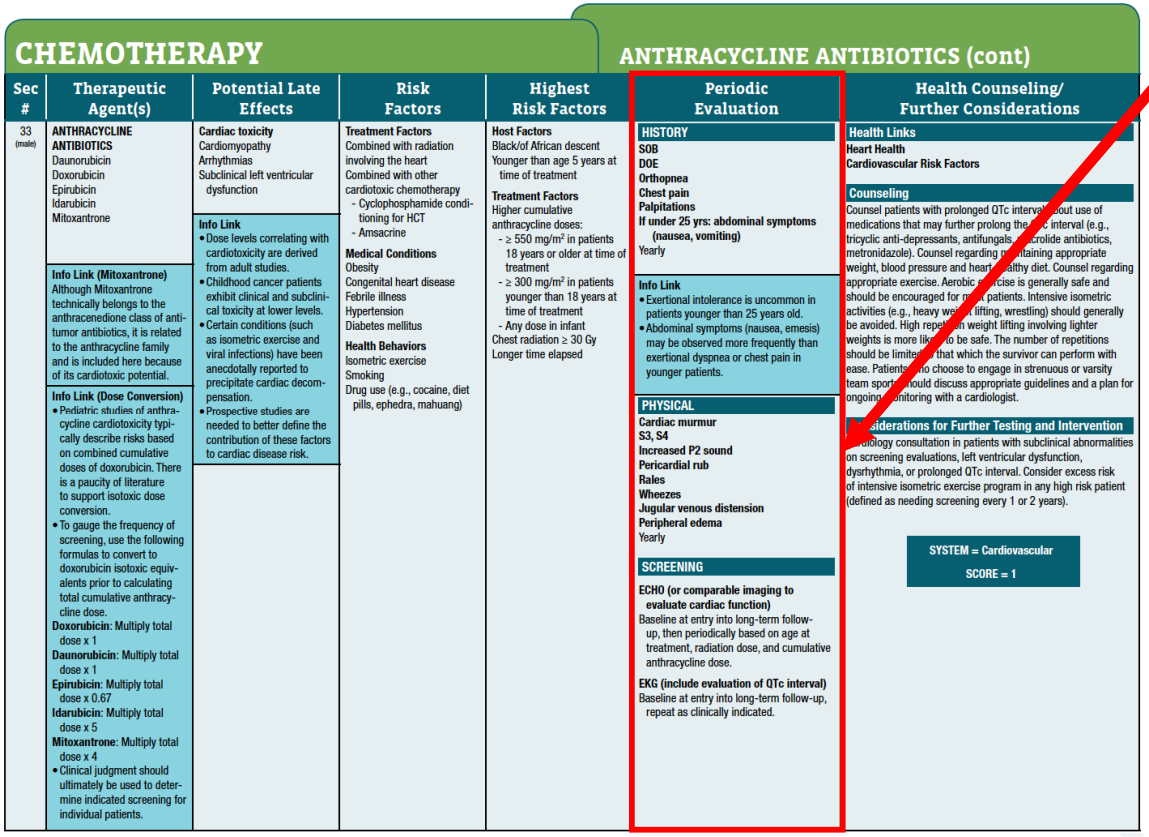

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- Suggested evaluations are then outlined pertinent to the exposure and degree of risk

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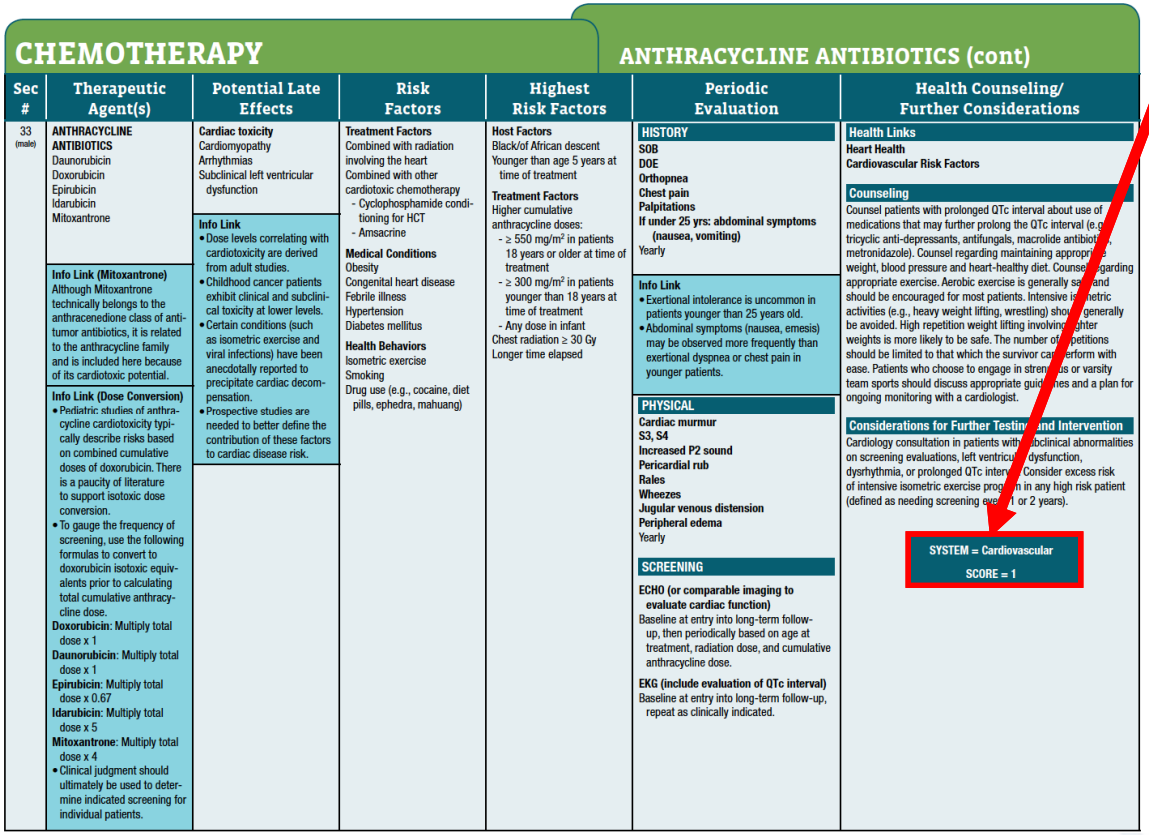

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- Lastly, the level of evidence is scored according to the National Comprehensive Cancer Network "Categories of Consensus"

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Pertinent Upcoming CV Revisions

- Cardiomyopathy surveillance for at risk survivors
- Doxorubicin equivalent anthracycline doses
- Pregnancy related cardiomyopathy surveillance
- Approach to exercise in at risk survivors (discussed separately)

Cardiomyopathy Surveillance in at Risk Survivors

RECOMMENDED FREQUENCY OF ECHOCARDIOGRAM (or comparable cardiac imaging)			
Age at Treatment*	Radiation with Potential Impact to the Heart§	Anthracycline Dose†	Recommended Frequency
<1 year old	Yes	Any	Every year
	No	< 200 mg/m²	Every 2 years
		≥ 200 mg/m²	Every year
1-4 years old	Yes	Any	Every year
	No	<100 mg/m²	Every 5 years
		≥100 to <300 mg/m²	Every 2 years
		≥300 mg/m²	Every year
≥5 years old	Yes	<300 mg/m²	Every 2 years
		≥300 mg/m²	Every year
	No	<200 mg/m²	Every 5 years
		≥200 to <300 mg/m²	Every 2 years
		≥300 mg/m²	Every year
Any age with decrease in serial function			Every year

*Age at time of first cardiotoxic therapy (anthracycline or radiation [see Section 80], whichever was given first)
§See Section 80
†Based on doxorubicin isotoxic equivalent dose [see conversion factors on previous page, "Info Link (Dose Conversion)"]

?

	Anthracycline dose	Chest radiation dose	Anthracycline + chest radiation
High	≥250 mg/m²	≥35 Gy	≥100 mg/m² (anthracycline) + ≥15 Gy (radiation)
Moderate	100 to <250 mg/m²	≥15 to <35 Gy	..
Low	<100 mg/m²	..	..

Table 3: **Definitions of cardiomyopathy risk groups**

Armenian et al, *Lancet Oncol* 2015; Blanco et al, *J Clin Oncol* 2012; Chow et al, *J Clin Oncol* 2015; Haddy, *Circ* 2016; Mulrooney, *Br Med J* 2009; Mulrooney, *Ann Intern Med* 2016; Ramjaun et al, *Pediatr Blood Cancer* 2015; Wong et al, *Ann Intern Med* 2014; Yeh et al, *Ann Intern Med* 2014

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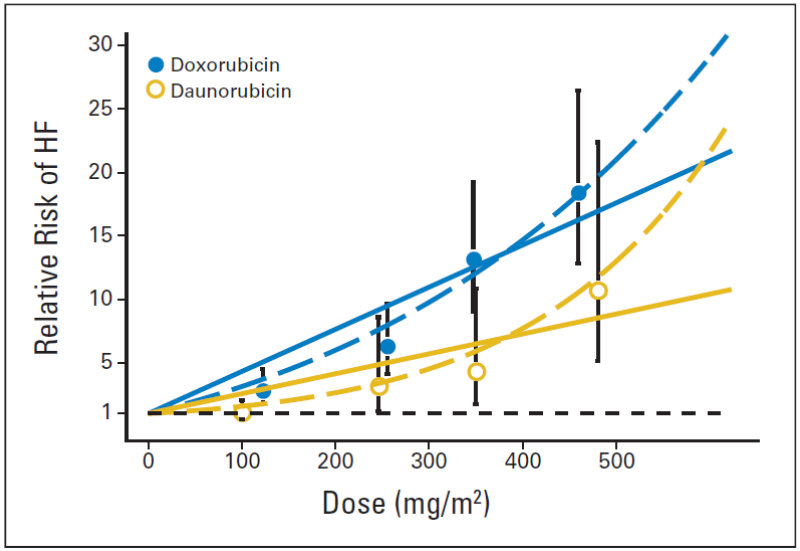
Doxorubicin Equivalent Anthracycline Doses



Feijen et al, *J Clin Oncol* 2015

Model and Dose Category	Daunorubicin-to-Doxorubicin Ratio			
	Ratio	95% CI	Mean	95% CI
Primary model*			0.45	0.23 to 0.73
None	—			
≤ 0.1 to < 200 mg/m²	0.39	0.04 to 0.78		
≤ 200 to < 300 mg/m²	0.50	0.00 to 1.12		
≤ 300 to < 400 mg/m²	0.33	0.03 to 0.62		
≤ 400 mg/m²	0.58	0.09 to 1.12		
Secondary model†			0.41	0.29 to 1.28‡
None	—			
≤ 0.1 to < 150 mg/m²	0.34	0.14 to 2.60‡		
≤ 150 to < 300 mg/m²	0.30	0.21 to 1.37‡		
≤ 300 mg/m²	0.58	0.25 to 1.08‡		

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Pregnancy Related Cardiomyopathy Surveillance

- Women with no prior history of cardiac dysfunction and normal cardiac function at the outset of pregnancy are at low risk to develop pregnancy-induced cardiomyopathy
  - Hines et al, J Cancer Surviv 2016; van Dalen et al, Eur J Cancer 2006

Pregnancy Related Cardiomyopathy Surveillance

- Echocardiogram at pre- or early-pregnancy baseline for patients who received: 1) ≥250 mg/m^2 anthracyclines, 2) ≥35 Gy chest radiation, or 3) any dose of anthracycline plus any dose of chest radiation who are pregnant or planning to become pregnant
- If no prior abnormalities and normal pre-/early-pregnancy echo, follow-up echocardiograms may be obtained at the treating provider's discretion
- Those with abnormalities prior to pregnancy or on pre-/early-pregnancy baseline echo are at highest risk for pregnancy-associated cardiomyopathy and should be monitored periodically during pregnancy and during labor and delivery due to risk of cardiac failure

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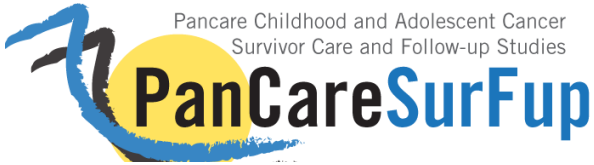
Pancare Childhood and Adolescent Cancer
Survivor Care and Follow-up Studies
PanCareSurFup


CHILDREN'S
ONCOLOGY
GROUP
Foundation


International Guideline
Harmonization Group
for Late Effects of Childhood Cancer


Children's
Cancer and
Leukaemia
Group
Working together to
beat childhood cancer


DCOG LATER
Longterm effects after childhood cancer


SIGN
Scottish Intercollegiate Guidelines Network


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International Guideline Harmonization Group

Recommendations for cardiomyopathy surveillance for survivors of childhood cancer: a report from the International Late Effects of Childhood Cancer Guideline Harmonization Group

Saro H Armenian, Melissa M Hudson, Renee L Mulder, Ming Hui Chen, Louis S Constine, Mary Dwyer, Paul C Nathan, Wim J E Tissing, Sadhna Shankar, Elske Sieswerda, Rod Skinner, Julia Steinberger, Elvira C van Dalen, Helena van der Pal, W Hamish Wallace, Gill Levitt, Leontien C M Kremer

Armenian et al, *Lancet Oncol* 2015

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