Evidence of Infusion Duration of Anthracyclines, Does It Matter to the Heart?

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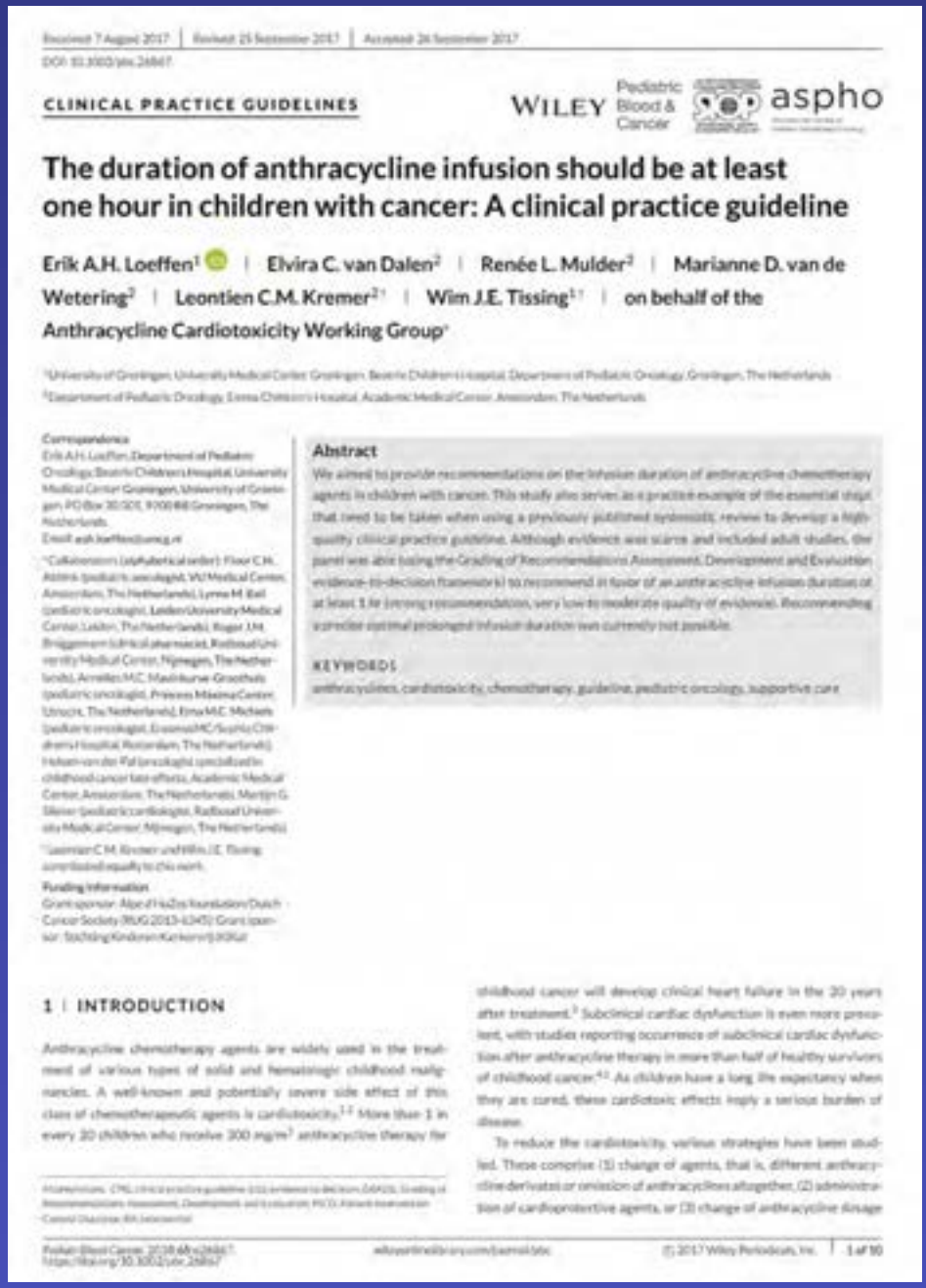
Conflict of interest

- Nothing to disclose

Content



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CLINICAL PRACTICE GUIDELINES

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The duration of anthracycline infusion should be at least one hour in children with cancer: A clinical practice guideline

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Abstract

We aimed to provide recommendations on the infusion duration of anthracycline chemotherapy agents in children with cancer. This study also serves as a practical example of the essential steps that need to be taken when using a previously published systematic review to develop a high-quality clinical practice guideline. Although evidence was scarce and included adult studies, the panel was able (using the Grading of Recommendations Assessment, Development and Evaluation evidence-to-decision framework) to recommend in favor of an anthracycline infusion duration of at least 1 hr (strong recommendation, very low to moderate quality of evidence). Recommending a precise optimal prolonged infusion duration was currently not possible.

KEYWORDS
anthracyclines, cardiotoxicity, chemotherapy, guideline, pediatric oncology, supportive care

1 | INTRODUCTION

Anthracycline chemotherapy agents are widely used in the treatment of various types of solid and hematologic childhood malignancies. A well-known and potentially severe side effect of this class of chemotherapeutic agents is cardiotoxicity.[1,2] More than 1 in every 20 children who receive 300 mg/m^2 anthracycline therapy for childhood cancer will develop clinical heart failure in the 20 years after treatment.[3] Subclinical cardiac dysfunction is even more prevalent, with studies reporting occurrence of subclinical cardiac dysfunction after anthracycline therapy in more than half of healthy survivors of childhood cancer.[4,5] As children have a long life expectancy when they are cured, these cardiotoxic effects imply a serious burden of disease.

To reduce the cardiotoxicity, various strategies have been studied. These comprise (1) change of agents, that is, different anthracycline derivates or omission of anthracyclines altogether, (2) administration of cardioprotective agents, or (3) change of anthracycline dosage

Abbreviations: CPG, clinical practice guideline; EtD, evidence-to-decision; GRADE, Grading of Recommendations Assessment, Development and Evaluation; PICO, Patient-Intervention-Control-Outcome; RR, Intervention

What do we mean with ‘guidelines’?

“Trustworthy guidelines should be based on a systematic evidence review, developed by panel of multidisciplinary experts, provide a clear explanation of the logical relationships between alternative care options and health outcomes, and provide ratings of both the quality of evidence and the strength of the recommendations.”

Institute of Medicine (2011)

GRADE methodology

Quality of evidence

- Very low
- Low
- Moderate
- High

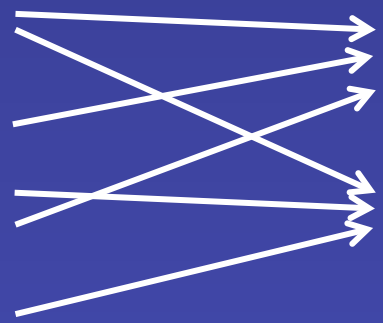
Strength of recommendation

- Weak
- Strong

GRADE methodology

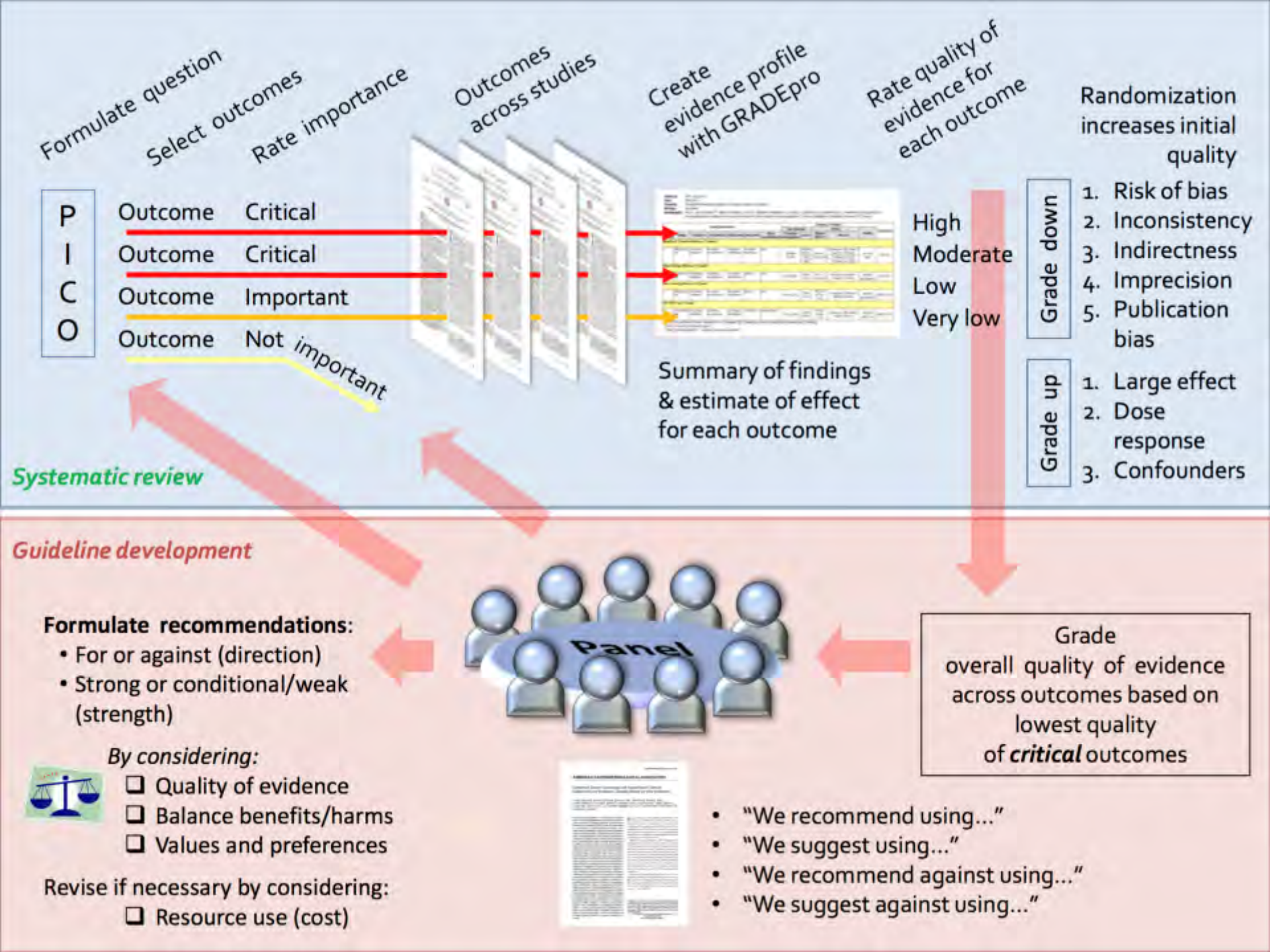
Quality of evidence

- Very low
- Low
- Moderate
- High



Strength of recommendation

- Weak
- Strong


Formulate question
Select outcomes
Rate importance
Outcomes across studies
Create evidence profile with GRADEpro
Rate quality of evidence for each outcome
P
I
C
O
Outcome Critical
Outcome Critical
Outcome Important
Outcome Not important
Summary of findings & estimate of effect for each outcome
High
Moderate
Low
Very low
Randomization increases initial quality
Grade down
1. Risk of bias
2. Inconsistency
3. Indirectness
4. Imprecision
5. Publication bias
Grade up
1. Large effect
2. Dose response
3. Confounders
Systematic review
Guideline development
Panel
Formulate recommendations:
• For or against (direction)
• Strong or conditional/weak (strength)
By considering:
❑ Quality of evidence
❑ Balance benefits/harms
❑ Values and preferences
Revise if necessary by considering:
❑ Resource use (cost)
Grade overall quality of evidence across outcomes based on lowest quality of critical outcomes
• "We recommend using…"
• "We suggest using…"
• "We recommend against using…"
• "We suggest against using…"

PICO A & PICO B

Patient	Children with cancer receiving anthracyclines	
Intervention	A. ≥1 hour	B. ≥6 hours
Control	A. push (<1 uur)	B. 1-6 hours
Outcome	Clinical heart failure, Subclinical heart failure, Tumour response, Progression-free survival, Overall survival, Adverse effects other than cardiac Damage, Quality of life, Costs	

Evidence

Different dosage schedules for reducing cardiotoxicity in people with cancer receiving anthracycline chemotherapy (Review)

van Dalen EC, van der Pal HJH, Kremer LCM

803 participants

n = 82 *n* = 52 *n* = 240 *n* = 62 *n* = 178 *n* = 145 *n* = 44

Adult studies
n = 374

Age nm
n = 62

Pediatric studies
n = 367

Evidence

Different dosage schedules for reducing cardiotoxicity in people with cancer receiving anthracycline chemotherapy (Review)

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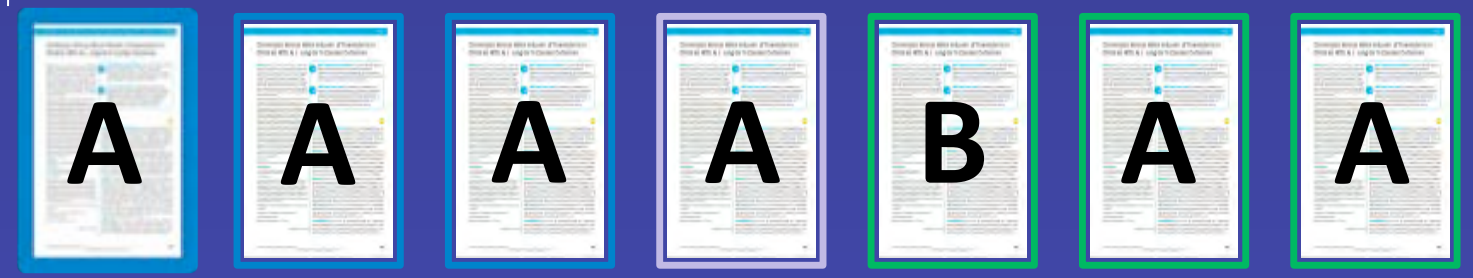

n = 82	*n* = 52	*n* = 240	*n* = 62	*n* = 178	*n* = 145	*n* = 44
5-10min vs 72u	15min vs 48u	bolus vs 96u	15-20min vs 6u	1u vs 24u	15min vs 48u	push vs 48u

Evidence overview, first PICO B

- ≥6 hours vs. 1-6 hours

Pediatric

TABLE 3.

PICO 2. ≥6 hours vs. 1-6 hours, evidence table for **pediatric** studies who studied this question.

Outcome	No. of studies	No. of participants	Follow up (median, range)	Anthracycline, cumulative dose infusion times	Events	Statistical method	Effect size	Quality of evidence
1. Clinical heart failure	1; Escherich 2007	178	7 days	daunorubicin, 36 vs 36, **24 hours vs. 1 hour**	0/93 vs. 0/85	Risk ratio (95% CI)	Not estimable	⊕⊕◯◯ LOW[1]
2. (Sub)clinical heart failure combined	1; Escherich 2007	178	7 days[2]	daunorubicin, 36 vs 36, **24 hours vs. 1 hour**	0/93 vs. 0/85	Risk ratio (95% CI)	Not estimable	⊕⊕◯◯ LOW[1]
3. Subclinical cardiac dysfunction as a continuous outcome	0							
4. Response rate[3]	1; Escherich 2007	178	7 days	daunorubicin, 36 vs 36, **24 hours vs. 1 hour**	51/93 vs. 38/85	Risk ratio (95% CI)	1.23, 95% CI 0.91 to 1.66	⊕⊕◯◯ LOW[1]
5. Overall survival	0							
6. Adverse effects other than cardiac damage	0							
7. Quality of life	0							

[1] (Escherich 2007) GRADE Quality assessment = study design is randomised trials, inconsistency and indirectness not serious, downgraded two levels because of serious risk of imprecision (neither criterion for precision is met) and serious risk of bias (Random sequence generation (selection bias) unclear, allocation concealment (selection bias) unclear, performance bias unclear, detection bias unclear, attrition bias high, reporting bias high, other bias unclear), other considerations none

[2] Study performed between 1992 and 1994, article published in 2007, stating: *"No specific analysis of toxicity was performed in this study. However, evaluation of the regular documentation form of the COALL study did not show more mucositis in the long-term infusion group. This form also asks for signs of cardiac insufficiency. So far no patient in the randomized DNR infusion groups was reported to have developed clinical signs of cardiac insufficiency or decrease of shortening fraction below 25 %."*

[3] Event is defined as good response

Adult

TABLE 4.

PICO 2. ≥6 hours vs 1-6 hours, evidence table for **adult** studies who studied this question.

Outcome	No. of studies	No. of participants	Follow up (median, range)	Anthracycline, cumulative dose infusion times	Events	Statistical method	Effect size	Quality of evidence
1. Clinical heart failure	0							
2. (Sub)clinical heart failure combined	0							
3. Subclinical cardiac dysfunction as a continuous outcome	0							
4. Response rate	0							
5. Overall survival	0							
6. Adverse effects other than cardiac damage	0							
7. Quality of life	0							

PICO B: ≥6 hours vs 1-6 hours

- 1 pediatric study included, n=178
  - Follow-up = 7 days
  - No (sub)clinical heart failure
  - Response rate (good response): 51/93 vs. 38/85, RR 1.23, 95% CI 0.91 to 1.66
- no adult studies included

The panel reluctantly admitted formulating a recommendation was not possible

Evidence overview, PICO A

- ≥1 hour vs. push (<1 hour)

Pediatric

TABLE 1.

PICO 1. ≥1 hour vs. push, evidence table for **pediatric** studies who studied this question.

Outcome	No. of studies	No. of participants	Follow up (median, range)	Anthracycline, cumulative dose in mg/m² (median), infusion times	Events	Statistical method	Effect size	Quality of evidence
1. Clinical heart failure	1; Lipshultz 2002	121	1.5 years, 0-4.7 years[1]	doxorubicin, 340 vs 336, **48 hours vs. less than 1 hour ("basically within 15 minutes")**	0/57 vs. 0/64	Risk ratio (95% CI)	Not estimable	⊕⊕◯◯ LOW[4]
2. (Sub)clinical heart failure combined	0							
3. Subclinical cardiac dysfunction as a continuous outcome	2 (pooling not possible); 1) Steinherz 1993 2) Lipshultz 2002	1) 44 2) 121	1) 54+ months (minimal 25+ months) 2) 1.5 years, 0-4.7 years[1]	1) daunorubicin, 400 vs 360, **48 hours vs. push** 2) doxorubicin, 340 vs 336, **48 hours vs. less than 1 hour ("basically within 15 minutes")**	1) median change in LVSF +1 vs. -6.5 2) multiple median z-scores[2]	1) nm 2) nm	1) Significance not stated 2) Not significant	⊕⊕◯◯ LOW[5]
4. Response rate	0							
5. Overall survival	0[3]							
6. Adverse effects other than cardiac damage	0							
7. Quality of life	0							

Adult

TABLE 2.

PICO 1. ≥1 hour vs. push, evidence table for **adult** studies who studied this question.

Outcome	No. of studies	No. of participants	Follow up (median, range)	Anthracycline, cumulative dose infusion times	Events	Statistical method	Effect size	Quality of evidence
1. Clinical heart failure	4; 1) Casper 1991 2) Hortobagyi 1989 3) Shapira 1990 4) Zalupski 1991	1) 82 2) 52 3) 62 4) 240	1) 50 months*, nm 2) nm 3) nm 4) nm	1) doxorubicin, nm vs. 420, **72h vs. 5-10 min** 2) epirubicin, 630 vs. 540, **48h vs. 15 min** 3) doxorubicin, 428 vs. 410, **6h vs. 15-20 min** 4) doxorubicin, 221 vs 240, **96h vs. bolus**	1) 2/43 vs. 2/39 2) 1/27 vs. 3/25 3) 0/31 vs. 4/31 4) 1/122 vs. 10/118 Total = 4/223 vs. 19/213	Risk ratio (95% CI)	Total 0.22 (0.08-0.60)	⊕⊕⊕◯ MODERATE[1]
2. (Sub)clinical heart failure combined, defined as:								
2.1 >=10% decrease in LVEF	1; Casper 1991	82	50 months*, nm	doxorubicin, nm vs. 420, **72h vs. 5-10 min**	16/43 vs. 19/39	Risk ratio (95% CI)	0.76 (0.46 - 1.26)	⊕◯◯◯ VERY LOW[2]
2.2 >=15% decrease in LVEF	1; Hortobagyi 1989	52	nm	epirubicin, 630 vs. 540, **48h vs. 15 min**	1/27 vs. 3/25	Risk ratio (95% CI)	0.31 (0.03 - 2.78)	⊕⊕◯◯ LOW[3]
2.3 a fall in LVEF of > 20%	1; Shapira 1990	62	nm	doxorubicin, 428 vs. 410, **6h vs. 15-20 min**	0/31 vs. 13/31	Risk ratio (95% CI)	0.04 (0.00 - 0.60)	⊕⊕⊕◯ MODERATE[4]
2.4 a decrease in LVEF	1; Zalupski 1991	240	nm	doxorubicin, 221 vs 240, **96h vs. bolus**	6/122 vs. 16/118	Risk ratio (95% CI)	0.36 (0.15 - 0.90)	⊕⊕⊕◯ MODERATE[5]
3. Subclinical heart failure as a continuous outcome	1; Shapira 1990	62	nm	doxorubicin, 428 vs. 410, **6h vs. 15-20 min**	Mean fall in LVEF = 4% vs. 17% and 6% vs. 21%**	Wilcoxon signed-rank test	P < 0.001 (for both doses)	⊕⊕◯◯ LOW[6]
4. Response rate* **	2; 1) Hortobagyi 1989 2) Zalupski 1991	1) 52 2) 240	1) nm 2) nm	1) epirubicin, 630 vs. 540, **48h vs. 15 min** 2) doxorubicin, 221 vs 240, **96h vs. bolus**	1) 7/27 vs. 3/25 2) 21/122 vs. 20/118 Total = 28/149 vs.	Risk ratio (95% CI)	Total 1.20 (0.65 - 2.22)	⊕◯◯◯ VERY LOW[7]

Outcome	No. of studies	No. of participants	Follow up (median, range)	Anthracycline, cumulative dose infusion times	Events	Statistical method	Effect size	Quality of evidence
1. Clinical heart failure	4; 1) Casper 1991 2) Hortobagyi 1989 3) Shapira 1990 4) Zalupski 1991	1) 82 2) 52 3) 62 4) 240	1) 50 months* nm 2) nm 3) nm 4) nm	1) doxorubicin, nm vs. 420, 72h vs. 5-10 min 2) epirubicin, 630 vs. 540, 48h vs. 15 min 3) doxorubicin, 428 vs. 410, 6h vs. 15-20 min 4) doxorubicin, 221 vs 240, 96h	1) 2/43 vs. 2/39 2) 1/27 vs. 3/25 3) 0/31 vs. 4/31 4) 1/122 vs. 10/118 Total = 4/223 vs. 19/213	Risk ratio (95% CI)	Total 0.22 (0.08-0.60)	⊕⊕⊕◯ MODERATE[1]

Anthracycline, cumulative dose infusion times

Events

Effect size

1) doxorubicin, nm vs. 420, 72h vs. 5-10 min
2) epirubicin, 630 vs. 540, 48h vs. 15 min
3) doxorubicin, 428 vs. 410, 6h vs. 15-20 min
4) doxorubicin, 221 vs 240, 96h vs. bolus

1) 2/43 vs. 2/39
2) 1/27 vs. 3/25
3) 0/31 vs. 4/31
4) 1/122 vs. 10/118

Total = 4/223 vs. 19/213

Total 0.22 (0.08-0.60)

Overall conclusions

Balance of consequences				
Undesirable consequences *clearly outweigh* desirable consequences in most settings ☐	Undesirable consequences *probably outweigh* desirable consequences in most settings ☐	The balance between desirable and undesirable consequences *is closely balanced or uncertain* ☐	Desirable consequences *probably outweigh* undesirable consequences in most settings ■	Desirable consequences *clearly outweigh* undesirable consequences in most settings ☐

Type of recommendation - infusion duration of anthracycline chemotherapy: 1 hour or more vs. push infusion			
We recommend against offering this option	We suggest not offering this option ☐	We suggest offering this option ☐	We recommend offering this option ■

- We recommend an infusion duration of 1 hour or more for anthracycline chemotherapy in children with cancer. (strong recommendation, very low quality evidence)

Take home messages

- Don’t push it
- Strong recommendation possible with limited evidence + multidisciplinary panel
- As always: more evidence is needed

That's it (for now)

THANK YOU

Questions?

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Entire project group

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