Prophylaxis treatment options for untreated children UNIVERSITÉ McMaster AVAI University with severe hemophilia: starting time and dose This document prepares the clinician to discuss scientific evidence with the patient (or care taker) so they can make an informed decision together. Decision 1: What are the options for when to start prophylaxis? **Early:** before or at least after the first joint bleed or during the 1st or 2nd year of age, whichever comes first. **Late:** after 2 or more joint bleeds *or* at 3 years of age or older. Note: in the literature, early is usually called "primary" and late is usually called "secondary"; but we recommend against using these terms in clinical encounters. Why do parent preferences matter when making this decision? There are pros and cons to early start compared to late start: PROS of early start: CONS of early start: · Opportunity to prevent joint damage • Need for venous access and related problems (infections, blockage, Decreased anxiety about bleeding thrombosis, inhibitors, increased anxiety) · Potential reduction of subclinical bleeding or rare life-threatening bleeds • Increased treatment burden Other • Other: Selection of the best available studies (November 2012) **Benefits Risks** of early start compared to late start of early start compared to late start Joint health Venous access problems Outcomes after 4 years in 24 patients:1

	Age (y) at start of prophylaxis		Orthopedic score (0=normal)	
Early	1-2	1	0	
Late	3-6	6	4	
	>6	10	8	

<1 joint bleeds/year while on prophylaxis for all groups

Outcomes after 10 years in 21 patients:²

	# joint bleeds/year	Patients with clinically evident joint disease		
Early	1	0		
Late	3	15%		

Outcomes after 17 years in 76 patients:³

	Age (y) at start of prophylaxis	# joint bleeds/ year	Patients with clinically evident joint disease
Early	1-3	not reported	53%
Late	>3	not reported	79%

Patients in all groups had first joint bleeding at 1st year of age

Parental reassurance

- Once their child was on prophylaxis, parents had:
 - more confidence to let their child undertake
 - more vigorous activities
 - less concerns about their child.⁴

- Older children (4 years old) are more likely to infuse into peripheral veins compared to younger children (2 years old) who more often require an implantable central venous access device (CVAD).⁵
- Older children might also better accept the infusion and require less time.
- CVADs are associated with:
 - ➤ complications
 - high risk of infection: rate of 0.66 per 1,000 catheter-days⁶
 - of 53 children with CVADs, 30% experienced complications after 18 months⁷
 of 15 children with CVADs, 53% had deep vein thrombosis after 5½ years⁸
 - In the children with CVADS, 55% had deep vein thrombosis after 5½ year
 Ineed for rigorous training and frequent care⁹

Imited physical activity (for tunneled CVADs only).⁹

Risk of inhibitor development in 125 patients¹⁰

Age, months (n) at start of prophylaxis	Developed inhibitors		
<1 (35)	26%		
1-6 (15)	25%		
6-12 (37)	21%		
12-18 (19)	20%		
>18 (19)	9%		

Note: patients at high risk for inhibitor development might have developed inhibitors *before* starting prophylaxis. Also, the protective effect of prophylaxis compared to on dmand treatment should not be confused with the comparison of early versus late start of prophylaxis.

Risk of incomplete treatment

For prophylaxis to be effective, infusions should not be missed.¹¹ Of 34 families, 70% missed infusions primarily because of:

- time commitment for 58%
- uncooperative child for 8%.12

References: ¹Kreuz W Haemophilia 1998; ²Gringeri A J Thromb Haemost 2011; ³Fischer K Blood 2002; ⁴Beeton K Haemophilia 2007; ⁵Van Dijk K Haematologica 2004; ⁶Valentino LA Haemophilia 2004; ⁷Ljung R Acta Paediatr 1998; ⁸Journeycake JM Blood 2001; ⁹Santagostino E Haemaphilia 2010; ¹⁰Chalmers Haemophilia 2007; ¹¹Colllin PW J Thromb Haemost 2009; ¹²Hacker MR Haemophilia 2001

Decision 2: What are the options for prophylaxis dosing regimens?

Regimen	Dose		
High treatment dose, e.g. full-dose/Malmo protocol ¹	24-40 IU/kg x 3 weekly or 30-40 IU/kg x 2 weekly		
Intermediate dose	15-25 IU/kg x 2 or 3 weekly		
Tailored dose, e.g. escalating dose	Step 1: 50 IU/kg weekly; if bleeding, proceed to Step 2: 30 IU/kg x 2 weekly; if bleeding, proceed to Step 3: 25 IU/kg every other day		
Very low dose started before the first bleed, e.g. Kurnik protocol ²	25 IU/kg weekly as soon as notice bleeding tendency, for approximately 50 weeks; then switch to a higher dose		

Why do parent preferences matter when making this decision?

High dose provides better joint protection.

Low dose regimens require less frequent injections.

> Less frequent injections may prevent the need for venous access devices.

Selection of the best available studies (as of November 2012)

Option	Benefits			Risks		
	Joint health after 17 years in 128 patients ³			Venous access problems in 53 patients ⁴		
High or full dose		Patients without joint bleeds	Patients with healthy joints		F !!	Need of central venous access
	Full	36%	95%		Tailored	29%
	Intermediate	7%	31%	See p centr	See prior page (decision 1) for problems associated with entral venous access.	
Intermediate dose				Joint impairment Of 27 children on intermediate dose, 30% had significant breakthrough bleeding and required an increase in dose, and 7% required daily prophylaxis to reduce bleeding episodes. ⁷		
	Joint health ^₄		Joint impairment			
Tailored	Patients without bleeds (joint, central nervous system, or requiring hospitalization) Full 44% Tailored* 57%**		Risk of subjecting patients to some target joint development before escalation of therapy. ^{6,8}			
	Protective effect on inhibitor development in 56 patients ² Developed inhibitors		Trigger events Must delay activities associated with inhibitor development, e.g. surgery, vaccination, treating bleeds with intense clotting factor therapy. ⁹			
Very low dose						
	Full	4/%		Risk of joint bleeds		
	Note: Data is based on limited evidence from a single study, and was		The efficacy of very low dose prophylaxis in preventing joint bleeds has			
	not confirmed by a recei	ntly stopped unpublishe	ed trial.			

References: ¹Nilsson IM *J Intern Med* 1992; ²Kurnik K *Haemopilia* 2010; ³Fischer K *Haemopilia* 2002; ⁴Dodd C *Haemopilia* 2012; ⁵Blanchette VS *Haemopilia* 2010; ⁶Feldman BM *J Thromb Haemost* 2006; ⁷Liesner RJ *Br J Haematology* 1996; ⁸Carcao M *Haemophilia* 2010; ⁹Astermark J *Haemophilia* 2010

How much confidence can we have in these results for these 2 decisions?

We have to acknowledge that even the best available evidence about the starting time and dose regimen might be subject to bias because the stuies are observational and uncontrolled.