Prophylaxis treatment options for untreated children 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:
- Opportunity to prevent joint damage
- Decreased anxiety about bleeding
- Potential reduction of subclinical bleeding or rare life-threatening bleeds
- Other:_____

CONS of early start:
- Need for venous access and related problems (infections, blockage, thrombosis, inhibitors, increased anxiety)
- Increased treatment burden
- Other:_____

Selection of the best available studies (November 2012)

Benefits
of early start compared to late start

Joint health

Outcomes after 4 years in 24 patients:[1]

	Age (y) at start of prophylaxis	# joint bleeds 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]

Risks
of early start compared to late start

Venous access problems

- 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-days[6]
    - of 53 children with CVADs, 30% experienced complications after 18 months[7]
    - of 15 children with CVADs, 53% had deep vein thrombosis after 5½ years[8]
  - need for rigorous training and frequent care[9]
  - limited physical activity (for tunneled CVADs only).[9]

Risk of inhibitor development in 125 patients[10]

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

High or full dose

Benefits

Joint health after 17 years in 128 patients[3]

	Patients without joint bleeds	Patients with healthy joints
Full	36%	95%
Intermediate	7%	31%

Risks

Venous access problems in 53 patients[4]

	Need of central venous access
Full	75%
Tailored	29%

See prior page (decision 1) for problems associated with central venous access.

Intermediate dose

Risks

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]

Tailored dose

Benefits

Joint health[4]

	Patients without bleeds (joint, central nervous system, or requiring hospitalization)
Full	44%
Tailored*	57%**

*Of 56 children, 37% are on once weekly therapy, 34% are on twice weekly, 29% are on every other day after 5 years.[5]

**64% of Canadian cohort had healthy joints after 5 years at 1.2 joint bleeds per year.[6]

Risks

Joint impairment

Risk of subjecting patients to some target joint development before escalation of therapy.[6,8]

Very low dose

Benefits

Protective effect on inhibitor development in 56 patients[2]

	Developed inhibitors
Full	47%
Very low	4%

Note: Data is based on limited evidence from a single study, and was not confirmed by a recently stopped unpublished trial.

Risks

Trigger events

Must delay activities associated with inhibitor development, e.g. surgery, vaccination, treating bleeds with intense clotting factor therapy.[9]

Risk of joint bleeds

The efficacy of very low dose prophylaxis in preventing joint bleeds has *not* yet been fully established.

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