Centro di Riferimento Regionale
per la Cura dell'Emofilia e
delle Malattie Emorragiche Congenite

La profilassi nell'Emofilia

SISET Training Center

Corso Malattie Emorragiche

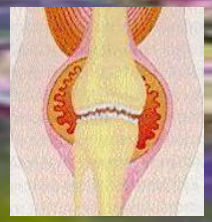
Firenze, 27 Settembre 2016

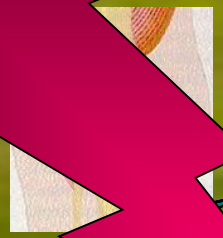
Annarita Tagliaferri
Centro di Riferimento Regionale per la Cura dell'Emofilia
Azienda Ospedaliero-Universitaria di Parma

Emofilia: obiettivi terapeutici

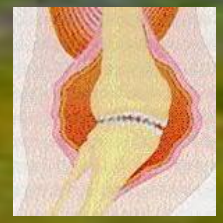
- L'emofilia è una malattia congenita cronica;
  non esiste, al momento, possibilità di guarigione
- Obiettivo terapeutico: prevenzione e trattamento delle manifestazioni emorragiche
- Nei paesi con disponibilità di concentrati efficaci e sicuri, l'obiettivo principale è la prevenzione delle emorragie e delle relative complicanze
- L'artropatia è la principale complicanza, causa di morbilità e fattore determinante per la qualità della vita

Emartro: problemi a lungo termine





SINOVITE ACUTA



EMARTRO

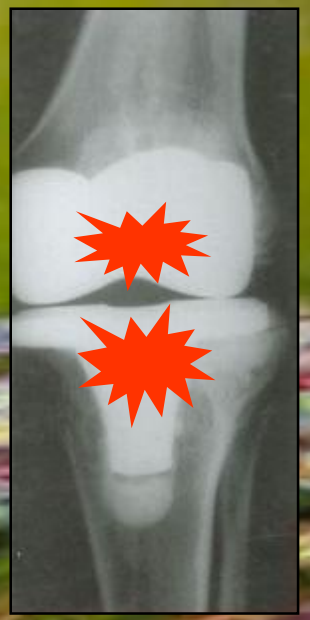
mediatori infiammatori,

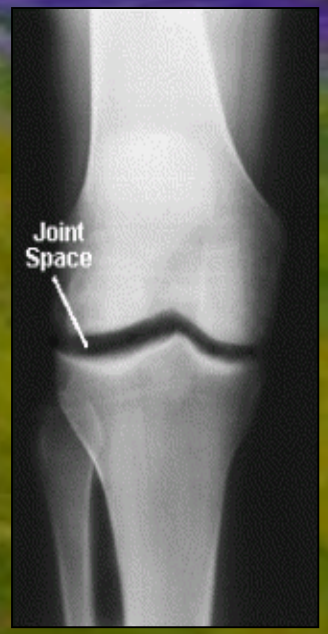
ARTROPATIA

SINOVITE CRONICA

La cartilagine è più suscettibile al danno indotto dalla presenza di sangue intra-articolare in giovane età ***Rosendaal, J Rheum, 2000***

qualità di vita





PREVENZIONE

DELL'ARTROPATIA

Haemophilia (2013), 19, e1–e47

Guidelines for the management of hemophilia

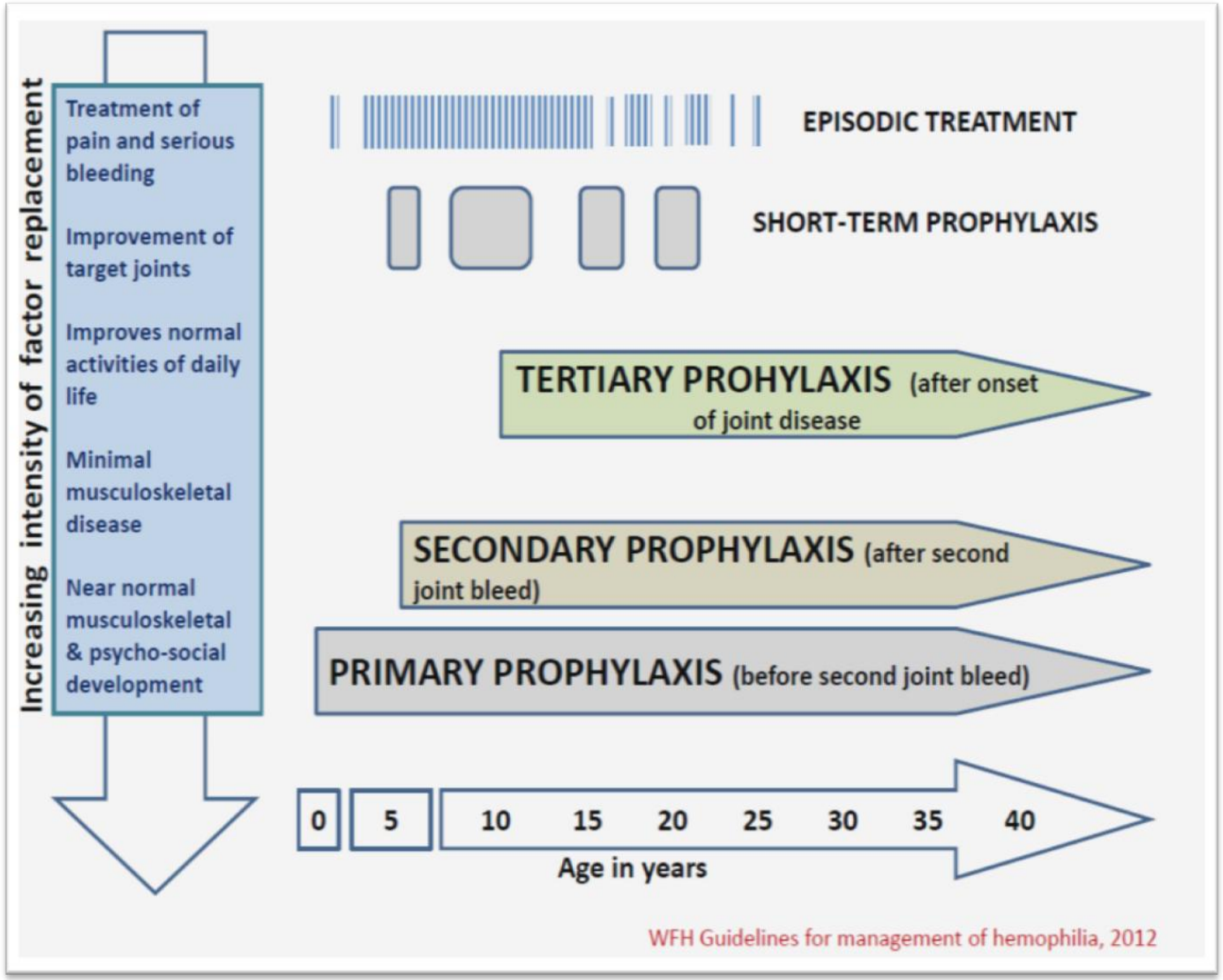
A. SRIVASTAVA,* A. K. BREWER,† E. P. MAUSER-BUNSCHOTEN,‡ N. S. KEY,§ S. KITCHEN,¶ A. LLINAS,** C. A. LUDLAM,†† J. N. MAHLANGU,‡‡ K. MULDER,§§ M. C. POON¶¶ and A. STREET***; TREATMENT GUIDELINES WORKING GROUP ON BEHALF OF THE WORLD FEDERATION OF HEMOPHILIA

Protocol	Definition
Episodic (on-demand treatment)	Treatment given at the time of clinically evident bleeding
Continuous prophylaxis	
Primary prophylaxis	Regular continuous[a] treatment initiated in the absence of documented osteochondral joint disease, determined by physical examination, and/or imaging studies, and started before the second clinically evident large joint bleed and at age 3 years[b]
Secondary prophylaxis	Regular continuous[a] treatment started after two or more bleeds into large joints[b] and before the onset of joint disease documented by physical examination and imaging studies
Tertiary prophylaxis	Regular continuous[a] treatment started after the onset of joint disease documented by physical examination and plain radiographs of the affected joints
Intermittent (periodic) prophylaxis	Treatment given to prevent bleeding for periods not exceeding 45 weeks in a year

Note: Recommendation of the scientific subcommittee on factor VIII and factor IX of the scientific and standardization committee of the International Society on Thrombosis and Haemostasis.[4]

[a]Continuous is defined as the intent of treating for 52 weeks per year and receiving a minimum of an a priori defined frequency of infusions for at least 45 weeks (85%) of the year under consideration.

[b]Large joints, ankles, knees, hips, elbows, and shoulders.


Increasing intensity of factor replacement
Treatment of pain and serious bleeding
Improvement of target joints
Improves normal activities of daily life
Minimal musculoskeletal disease
Near normal musculoskeletal & psycho-social development
EPISODIC TREATMENT
SHORT-TERM PROPHYLAXIS
TERTIARY PROHYLAXIS (after onset of joint disease
SECONDARY PROPHYLAXIS (after second joint bleed)
PRIMARY PROPHYLAXIS (before second joint bleed)
0
5
10
15
20
25
30
35
40
Age in years
WFH Guidelines for management of hemophilia, 2012

La profilassi può prevenire o rallentare l'evoluzione dell'artropatia emofilica...?

Gli emofilici moderati (FVIII/FIX > 1%) hanno una ridotta incidenza di emorragie e raramente sviluppano artropatia grave

Ramgren, 1962; Ahlberg, 1965

La profilassi può trasformare un emofilico grave in un emofilico moderato mantenendo valori di FVIII/IX > 1%.

Ridurre il numero degli episodi emorragici sin dall'infanzia può comportare una minore incidenza e gravità dell'artropatia

Nilsson, 1992

25 years' experience of prophylaxis in Sweden

	Cohort 1	Cohort 2	Cohort 3	Cohort 4	Cohort 5
Patients	6 (5 A, 1 B)	9 (8A, 1 B)	20 (17 A, 3 B)	10 (9 A,1 B)	15 (13 A, 2 B)
Present age (years)	3-6	7-12	13-17	18-23	24-32
Age at start of treatment (years)	1.1 (1-1.5)	1.2 (0.5-1.2)	2.6 (1-4.5)	4.9 (3-7)	7.0 (3-13)
Annual joint bleeds	0.1 (0-6)	0.1 (0-4)	3 (0.1-16.6)	5.6 (0.5-14)	5.0 (1.6-16)
Orthopaedic joint score	0	0	1.2 (0-7)	2.9 (0-7)	6.6 (0-15)
Pettersson score	0	0	4.8 (0-22)	14.2 (0-22)	20.6 (0-41)
Annual absence from school/work (days)			0.9 (0-6.7)	2.8 (0-9.8)	5.8 (1-20)

Data presented as means and ranges

Modified from Nilsson I.M. et al., J Intern Med 1992

Orthopedic Outcomes Study

Studio multicentrico internazionale in cui vengono valutati 477 pazienti affetti da emofilia grave di età <25 anni dei quali 411 in terapia "on-demand" e 66 in profilassi

I pazienti in profilassi a lungo termine, dopo un follow-up di 6 anni, presentavano oltre alla riduzione del numero emorragie articolari un outcome ortopedico migliore

Benefici sono stati riscontrati anche in pazienti con preesistente danno articolare.

La profilassi è associata ad un significativo:

- Minor numero di giorni di lavoro/scuola persi
- Minor numero di giorni di ricovero in ospedale

Aledort et al., J Intern Med, 1994

Reviews / Analyses

Modern treatment of haemophilia*

E. Berntorp,[1] V. Boulyjenkov,[2] D. Brettler,[3] M. Chandy,[4] P. Jones,[5] C. Lee,[6] J. Lusher,[7] P. Mannucci,[8] I. Peak,[9] K. Rickard,[10] & S. Seremetis[11]

Many rapid advances have been made in the diagnosis and therapy of haemophilia. Nevertheless, the condition still poses problems and challenges (e.g., joint disease, transfusion-transmitted diseases, inhibitors, provision of care in developing countries, and education and cost issues). WHO and the World Federation of Hemophilia held a joint meeting in Geneva, on 21–23 March 1994, to discuss and review current and future approaches to the management of haemophilia and its complications, including prospects for genetic technology and gene therapy in developed and developing countries. The present review article summarizes the discussions and recommendations made by the participants.

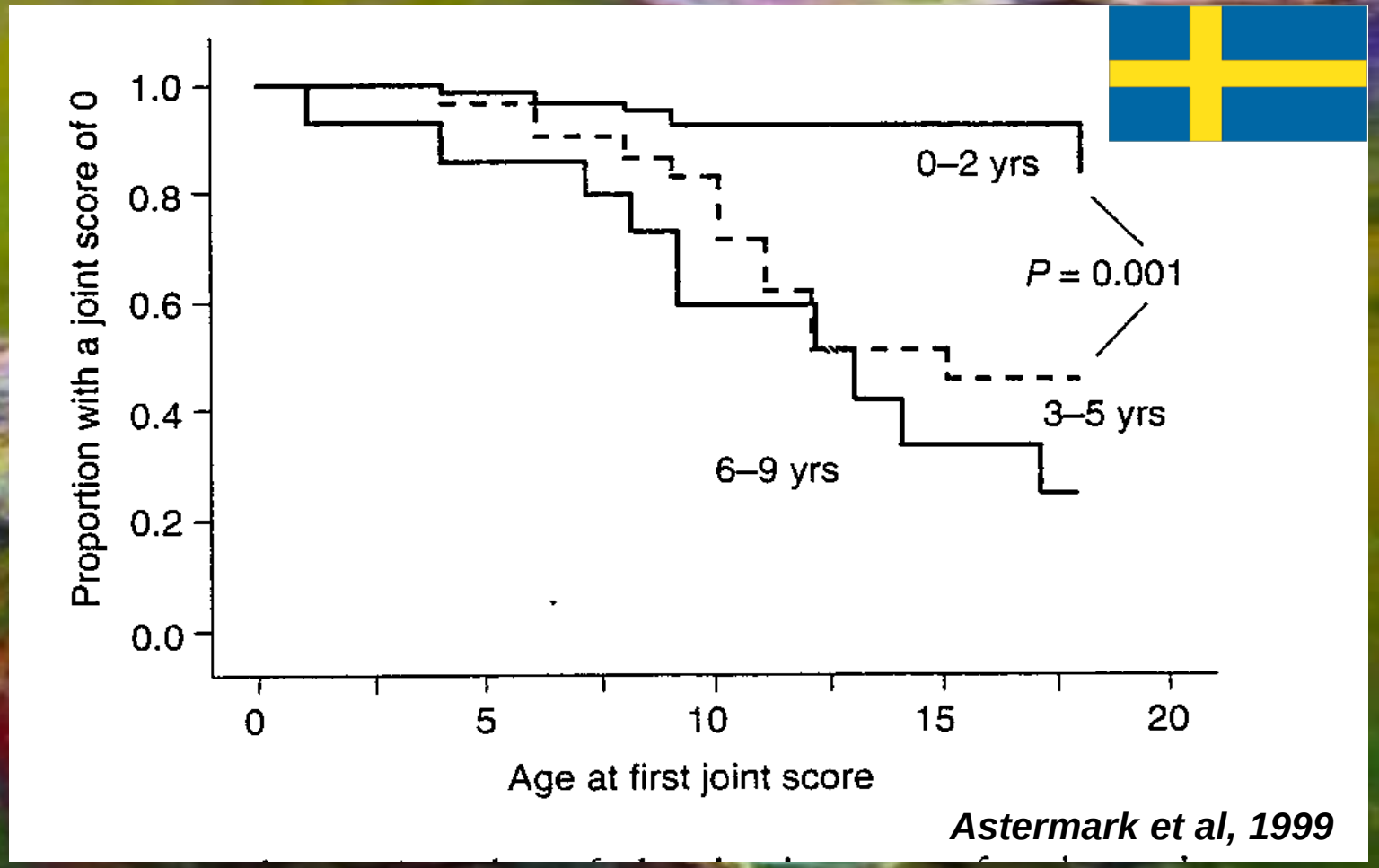
Recommendations

- Since the main goal is to prevent joint bleeding and its sequelae, prophylaxis should be considered as optimal management for persons with severe haemophilia A and B (baseline level <1% F VIII or F IX). Treatment should be started at 1–2 years of age and be continued indefinitely.

Bulletin of the World Health Organization, 1995, **73** (5): 691–701


When
to start?

Danno articolare ed età di inizio della profilassi



Astermark et al, 1999

Correlazione emorragia articolare/artropatia

	Group 1	Group 2	*Group 3*
Number of cases	8	6	7
Median age (yr) at start of prophylaxis	1.75	4.25	8.75
Median number of joint bleeds before start of prophylaxis	1	6	> 10
Joint bleeds during prophylaxis (median/year)	0.14	0.22	0.65
Orthopedic joint score			
1993	0	0	4
1997	0	4	8
Radiological joint score			
1993	0	0	11
1997	0	8	19.5

Kreutz et al., Haemophilia 1998

MASAC November 4, 2007

- Prophylaxis should be instituted early, prior to the onset of frequent bleeding, with the aim of keeping the trough FVIII or FIX level above 1% between doses
- Prophylaxis must be considered the optimal therapy for individuals with severe hemophilia A and B
- The individuals on prophylaxis have regular follow-up visits to evaluate joint status and to record any bleeding episodes that occur during prophylaxis
- No clear when to stop; joint bleeds with subsequent joint destruction are a lifelong problem for these individulas; therefore they may need to continue prophylaxis throughout their life

Il primo trial randomizzato

JOINT OUTCOME STUDY

The NEW ENGLAND JOURNAL of MEDICINE

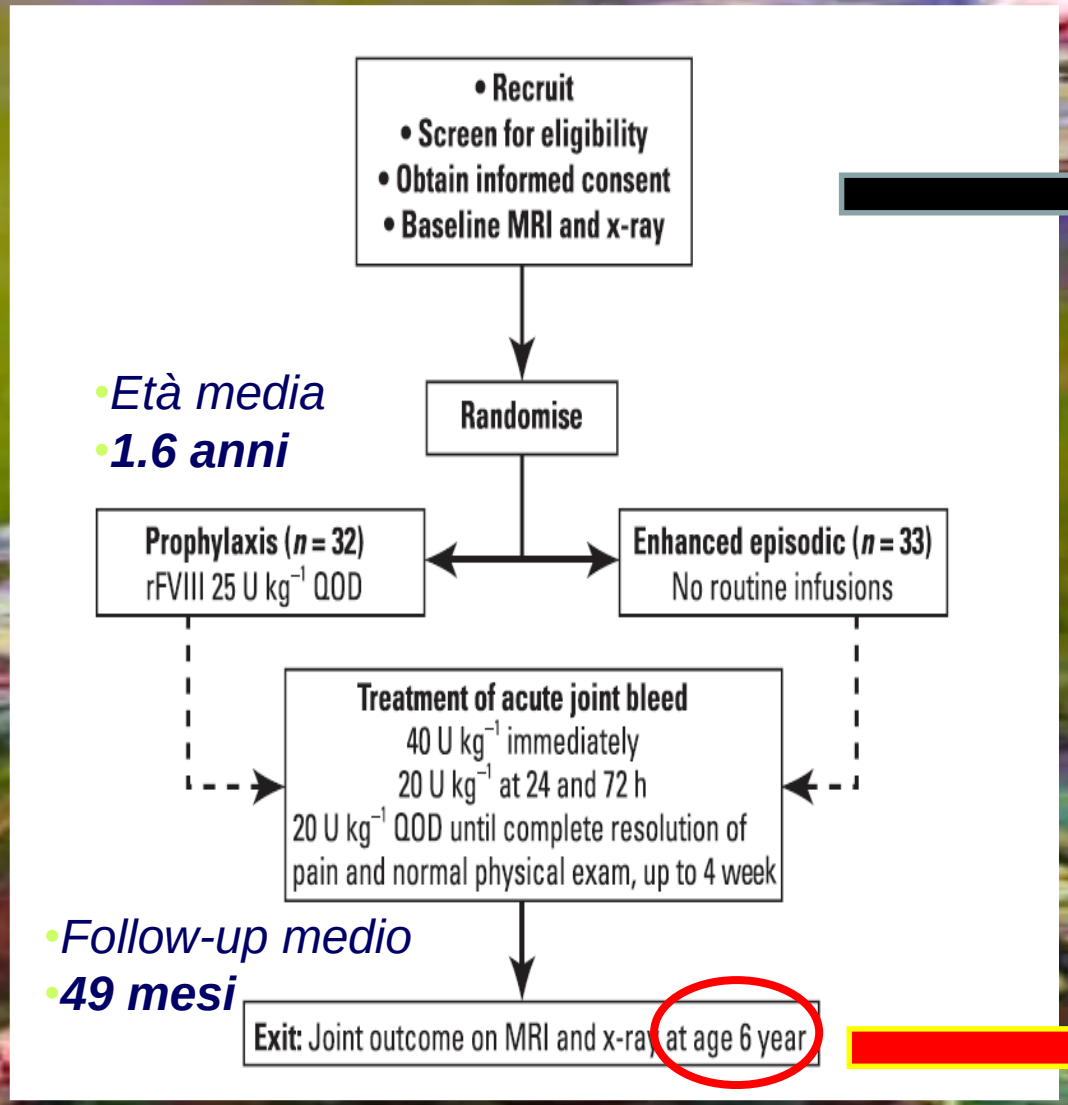
ESTABLISHED IN 1812 AUGUST 9, 2007 VOL. 357 NO. 6

Prophylaxis versus Episodic Treatment to Prevent Joint Disease in Boys with Severe Hemophilia

Marilyn J. Manco-Johnson, M.D., Thomas C. Abshire, M.D., Amy D. Shapiro, M.D., Brenda Riske, M.S., M.B.A., M.P.A., Michele R. Hacker, Sc.D., Ray Kilcoyne, M.D., J. David Ingram, M.D., Michael L. Manco-Johnson, M.D., Sharon Funk, B.Sc., P.T., Linda Jacobson, B.S., Leonard A. Valentino, M.D., W. Keith Hoots, M.D., George R. Buchanan, M.D., Donna DiMichele, M.D., Michael Recht, M.D., Ph.D., Deborah Brown, M.D., Cindy Leissinger, M.D., Shirley Bleak, M.S.N., Alan Cohen, M.D., Prasad Mathew, M.D., Alison Matsunaga, M.D., Desiree Medeiros, M.D., Diane Nugent, M.D., Gregory A. Thomas, M.D., Alexis A. Thompson, M.D., Kevin McRedmond, M.D., J. Michael Soucie, Ph.D., Harlan Austin, Ph.D., and Bruce L. Evatt, M.D.

Prospective, Multicentre (15 Centres)
Open-label, Randomized, Two arms
Enrollment: 08/1996-04/2005

JOS: design and endpoints



- *Età media*
- ***1.6 anni***

- *Follow-up medio*
- ***49 mesi***

- age ≤ 30 mo.
- FVIII ≤ 2 IU/dl
- ≤ 2 bleeds in each index joint
- normal joint imaging and motion
- FVIII inhibitor undetectable
- normal platelet count

PRIMARY OUTCOME:
Preservation of index joint structure (MRI/RX)
SECONDARY OUTCOMES:
n° of joint and total bleeds
n° of infusions
total FVIII IU

Manco-Johnson et al, N Engl J Med, 2007

Results

- Follow up 49 months (mean)

	Prophylaxis	On Demand
Number of enrolled patients	32	33
Number of evaluated patients	27	29
Good protocol adherence	96%	98%
Joint bleeds/year (mean) *	0.63	4.89
Total bleeds/year (mean) *	1.15	17.13
rFVIII use IU/Kg/year (mean) *	6000	2500
Primary outcome (no joint damage on Xray and MRI) **	93% RR 0.17	55% RR 6.1

* P <0.001 ** P 0.002

Manco-Johnson MJ, N Engl J Med, 2007

Results

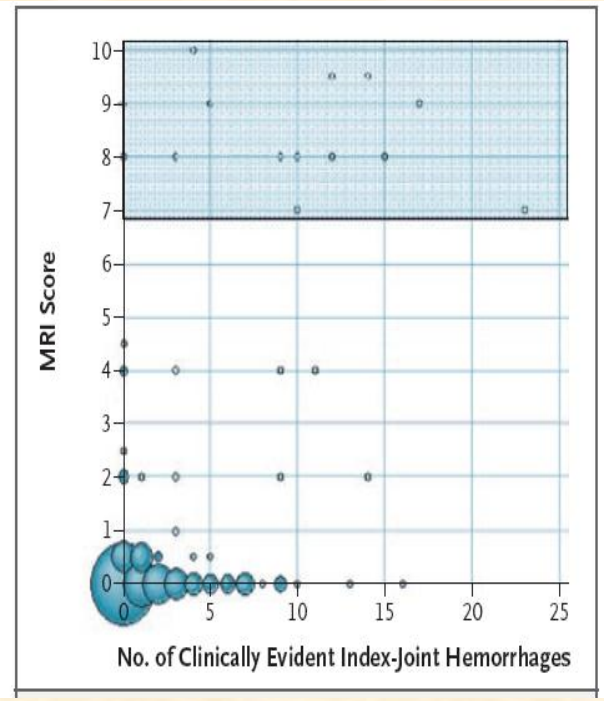
Manco-Johnson MJ, N Engl J Med, 2007

MRI is the preferable image technique:
more than half of the joint abnormalities were detected only by MRI and not by Radiography indicating that MRI is more sensitive.

Joint abnormalities, as determined by MRI, were not apparent on physical examination

Weak of evident correlation between hemarthroses and MRI scores:

- some joints with no hemorrhages had high MRI scores
- some joints with more than 10 hemorrahages didn't show damage on MRI



- Cronic microhemorrhage into the joints causes deterioration of joints without clinical evidence of hemarthroses.
- Prophylaxis prevents this subclinical process

Conclusion

To preserve joint health and prevent life-threatening hemorrhages

prophylaxis is justified

Manco-Johnson MJ, N Engl J Med, 2007

bjh guideline

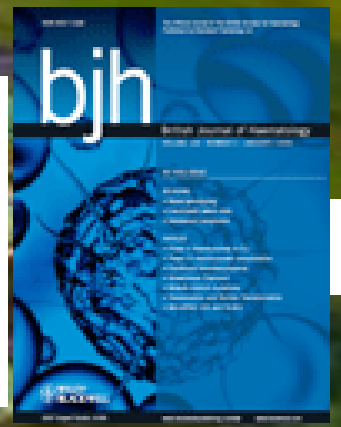
A United Kingdom Haemophilia Centre Doctors' Organization guideline approved by the British Committee for Standards in Haematology: guideline on the use of prophylactic factor VIII concentrate in children and adults with severe haemophilia A

Michael Richards,[1] Michael Williams,[2] Elizabeth Chalmers,[3] Ri Liesner,[4] Peter Collins,[5] Vicky Vidler[6] and John Hanley[7]
Writing group: on behalf of the Paediatric Working Party of the United Kingdom Haemophilia Doctors' Organisation

[1]St. James's University Hospital, Leeds, [2]Birmingham Children's Hospital, Birmingham, [3]Glasgow Sick Children's Hospital, Glasgow, [4]Great Ormond Street Hospital, London, [5]University Hospital of Wales, Cardiff, [6]Sheffield Children's Hospital, Sheffield, and [7]Newcastle Hospitals NHS Trust, UK

Recommendation

It is recommended that children with severe haemophilia receive prophylactic infusions of factor VIII with the aim of preventing haemarthroses and other bleeding episodes. (Recommendation grade 1A).



2010 Mar 11

Evaluation Study on Prophylaxis: a Randomised Italian Trial

Randomized controlled trial compared efficacy of prophylaxis with episodic therapy in preventing hemartroses and image-proven joint damage in children with severe haemophilia A, aged 1-7 years with negative Pettersson score, over 10 y

22 pts prophylaxis rFVIII 25 UI/Kg 3xweek

19 pts episodic therapy > 25UI/Kg every 12-24 h until complete resolution

AICE

ASSOCIAZIONE ITALIANA CENTRI EMOFILIA

Gringeri A., JTH 2011

A Randomized clinical trial of prophylaxis in children with haemophilia A (the ESPRIT study)

Results

- 21 Children on prophylaxis had fever hemartroses than 19 children on episodic therapy (median 0,20 vs 0.52 joint bleeding per pt; *P* <0.02)
- Plain-film radiology signs of arthropaty in 6 pts on prophylaxis (29%) vs 14 on-demand (74%) *P* < 0.05
- Prophylaxis was more effective when started early (<36months)
- 10 of 20 pts on prophylaxis required CVC
- 5 pts developed inhibitors (12.5%) 3 P (14.3%) 2 OD (10.5%)

Conclusions

This randomized trail confirms the efficacy of prophylaxis in preventing bleeds and arthropaty in children with hemophilia, particularly when it is initiated early in life

Gringeri A., JTH feb 2011

Controlled, cross-sectional MRI evaluation of joint status in severe haemophilia A patients treated with prophylaxis vs. on demand

Age at prophylaxis start (y)	Current age (y) 12 – 16	17 – 21	22 – 26	27 – 35	
< 2 (primary)	*3/4*	*8/8*	*5/9*	*3/4*	76%
2 – < 6 (secondary)	*2/4*	*3/7*	*1/5*	*3/6*	41%
6 – < 12 (secondary)	*n/a*	*1/12*	*2/12*	*0/3*	11%
12 – 18 (secondary)	*n/a*	*n/a*	*0/7*	*1/14*	5%
Never (on-demand)	*0*	*0/1*	*0/10*	*0/12*	0%

Oldenburg et al. *Haemophilia* 2015; 21: 171-79

Barriere alla profilassi

Costo dei concentrati

Età

Bleeding pattern

Profilassi

Non dimostrata alcuna correlazione (Giangrande; Haemophilia 2003)

Effetto protettivo profilassi precoce (Santagostino; BJH, 2005)

Profilassi associata a basso rischio di sviluppo inibitore (Gouw, Blood, 2007)

Dosage regimens

High dose

Haemophilia A: 25-40 IU/Kg 3 times/week
Haemophilia B: 25-40 IU/Kg 2 times/week

Intermediate dose

Haemophilia A: 15-25 IU/Kg 2 o 3 times/week
Haemophilia B: 30-50 IU/Kg 1 o 2 times/week

AICE Guidelines

Haemophilia A: 25-30 IU/Kg 3 times/week
Haemophilia B: 30-40 IU/Kg 2 times/week

Ottimizzare il regime

Raggiungere la dose ottimale gradualmente, incrementando progressivamente dose/frequenza settimanale, considerando la variabilità del fenotipo

Migliorare la compliance e l'accettazione delle famiglie

Ridurre il ricorso a CVAD

Swedish approach

For the Swedish group this is as a brief temporary step with the goal being to quickly escalate children to full prophylaxis:

Malmö: quicker escalation

Stockolm: more gradual escalation

Petrini, *Haemophilia* 2001

Canadian approach

Protocollo:	25 bambini con Emofilia A grave di età compresa fra 1 e 2.5 anni seguiti per 5 anni	
Criterio di valutazione:	Follow up a 3 mesi	3 emorragie nella stessa articolazione o 4 emorragie totali fanno ritenere che non vi sia un controllo adeguato del sanguinamento
Dose	1° step	50 UI/Kg 1 volta/settimana
	2° step	30 UI/Kg 2 volte/settimana
	3° step	25 UI/Kg a giorni alterni

Risultati dopo 5 anni di osservazione:

- il 32% dei bambini sono passati a due infusioni/settimana
- il 28% a giorni alterni
- il 40% ha sviluppato target joint
- media emorragie articolari: 1.2 /anno/per persona
- consumo medio coorte: 3656 UI/Kg/anno rFVIII

Feldmann B.M et al. J Thromb Haemost, 2006

Durata della profilassi

Secondo OMS e WFH è indefinita

Almeno fino ai 20 anni, cioè allo sviluppo completo delle ossa e delle articolazioni

Gringeri A, Haemophilia 2003 – Van den Berg HM, Haematologica 2004

Non chiaro se la profilassi primaria deve essere proseguita raggiunta l'età adulta, necessaria valutazione caratteristiche dei pazienti

Hay C.R.M, Haemophilia 2007

2010 Mar 11, UK guidlines on the use of prophylaxis

Prophylaxis in adolescent and adult patients

1 Adolescent and adult patients with severe haemophilia should be encouraged to continue regular prophylaxis at least until they have reached physical maturity. (Recommendation grade 2 B).

2 In some individuals who have demonstrated a much milder phenotype, adapting formal prophylaxis to a more targeted policy may be considered but in such cases, there must be an agreed plan for monitoring and reintroduction of prophylaxis if necessary. (Recommendation grade 2 C).

3 If significant haemarthroses occur after discontinuing prophylaxis, prophylaxis should be reinstituted to prevent joint damage and to maintain quality of life. Prophylaxis should, in particular, be restarted if bleeding interferes with education or employment. (Recommendation grade 2 C).

When discontinue prophylaxis…?

34 of 49 patients (mean age 20) discontinued prophylaxis	Permanently 11 pt	Temporarily 23 patients
Age at start	6.9	5.3
n° joint bleeds/year	2.8	6.2
Pettersson Score	8.0	8.0
Factor dose UI/Kg/week	22 (1144 Y)	37 (1924 Y)

Score to predict which patients might be able to safely stop prophylaxis utilizes:

- Age at start prophylaxis
- Joint bleeds/year on prophylaxis
- Weekly factor dose on prophylaxis

Fischer K, Hemophilia 2001

A Dutch-Danish study - follow-up: 80 patients - 3 years:
28 patients discontinued prophylaxis: 3.2 joint bleeds/y
52 patients continued on prophylaxis: 1.8 joint bleeds/y

van Dijk K., Fischer K, Br J Haematol, 2005

2010 Mar 11, UK guidlines on the use of prophylaxis

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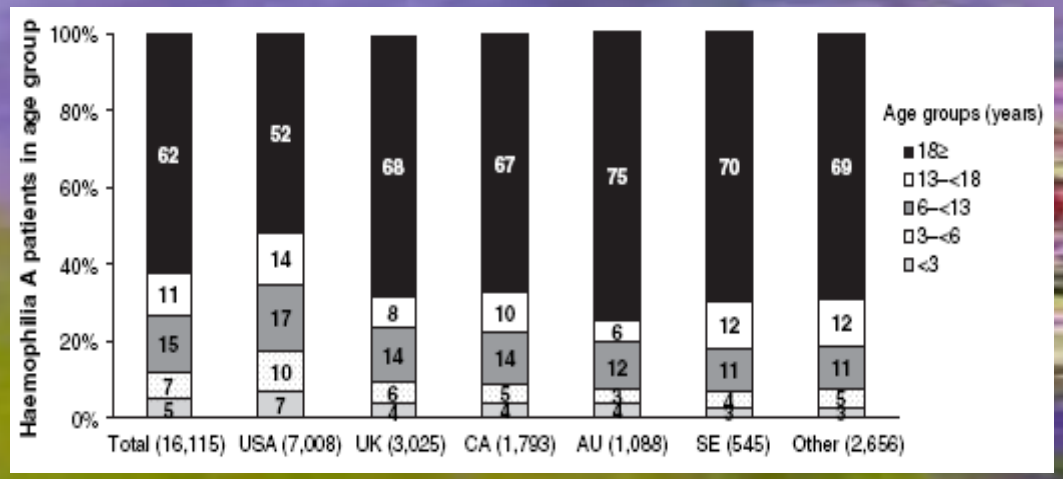
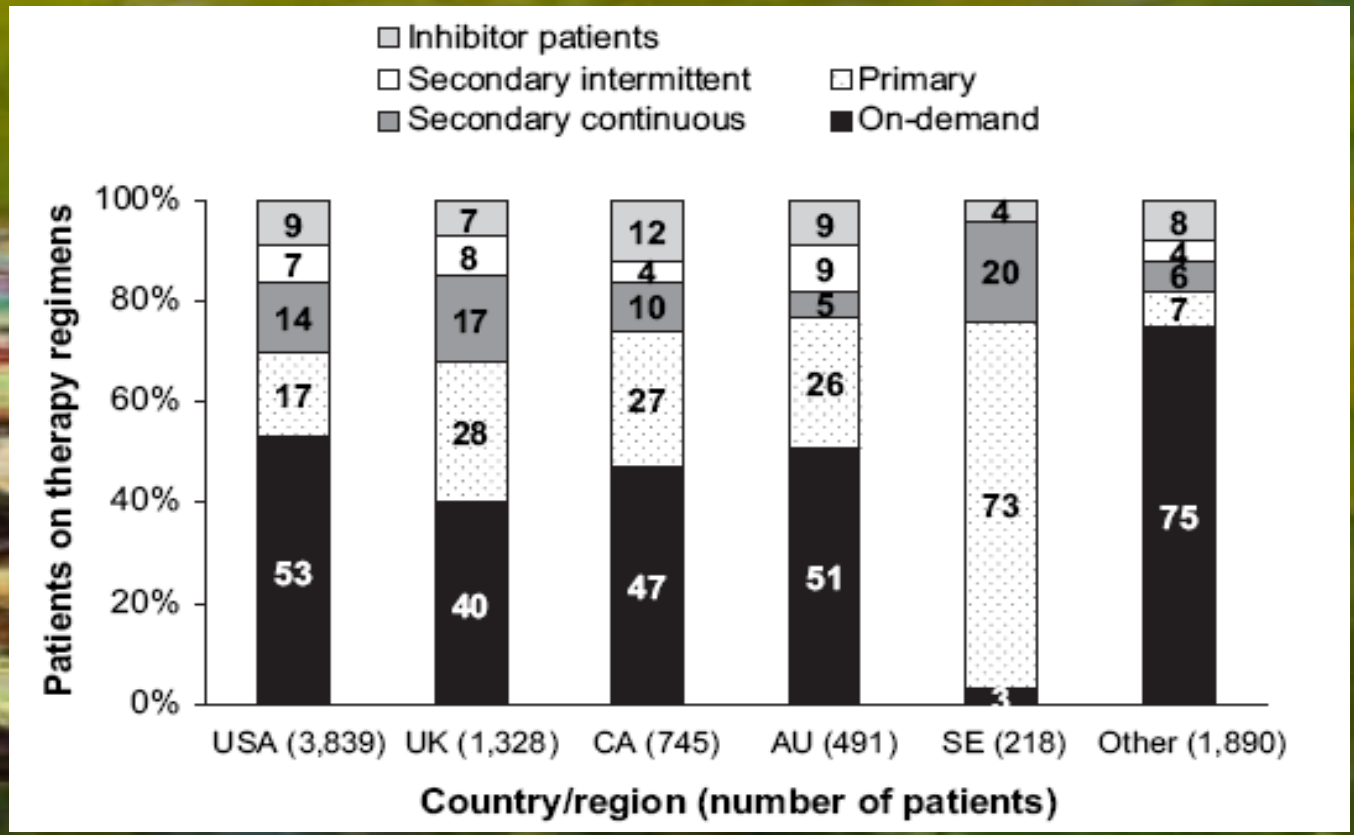


Practice patterns in haemophilia A therapy

(Geraghty et al, Haemophilia 2006)

Prophylaxis for all, indefinitely…?

147 HTCs >16,000 pts



The evolving scenario of haemophilia adult population

- **Young adults on primary prophylaxis with relatively healthy joints**

  → safely discontinue/modify prophylaxis?

- **Increasing number of adult patients with longer life expectancy**

  → effectively start / restart prophylaxis?

  → appropriate regimens?

  → emerging indications for newer bleeding risk?

Indicazioni alla profilassi nell'adulto

Prophylaxis most likely recommened to:

- Patients on primary prophylaxis with no or little joint damage.
- Patients experiencing life- or limb- threatening bleeding.
- Patients with frequent joint bleeding.

Walsh and Valentino, *Haemophilia* 2009

3 If significant haemarthroses occur after discontinuing prophylaxis, prophylaxis should be reinstituted to prevent joint damage and to maintain quality of life. Prophylaxis should, in particular, be restarted if bleeding interferes with education or employment. (Recommendation grade 2 C).

7 Short or long term secondary prophylaxis should be considered in patients with advanced arthropathy if recurrent bleeding episodes significantly interfere with work or mobility. (Recommendation grade 2 C).

Richards et al, UKHCDO, *Br J Haematol* 2010