4° CONVEGNO INTERREGIONALE
Attualità nel trattamento multidisciplinare dell'emofilia e delle altre coagulopatie emorragiche
CATANIA 15-16 Settembre 2018

LA TERAPIA SOSTITUTIVA NELL'ARTROPATIA EMOFILICA

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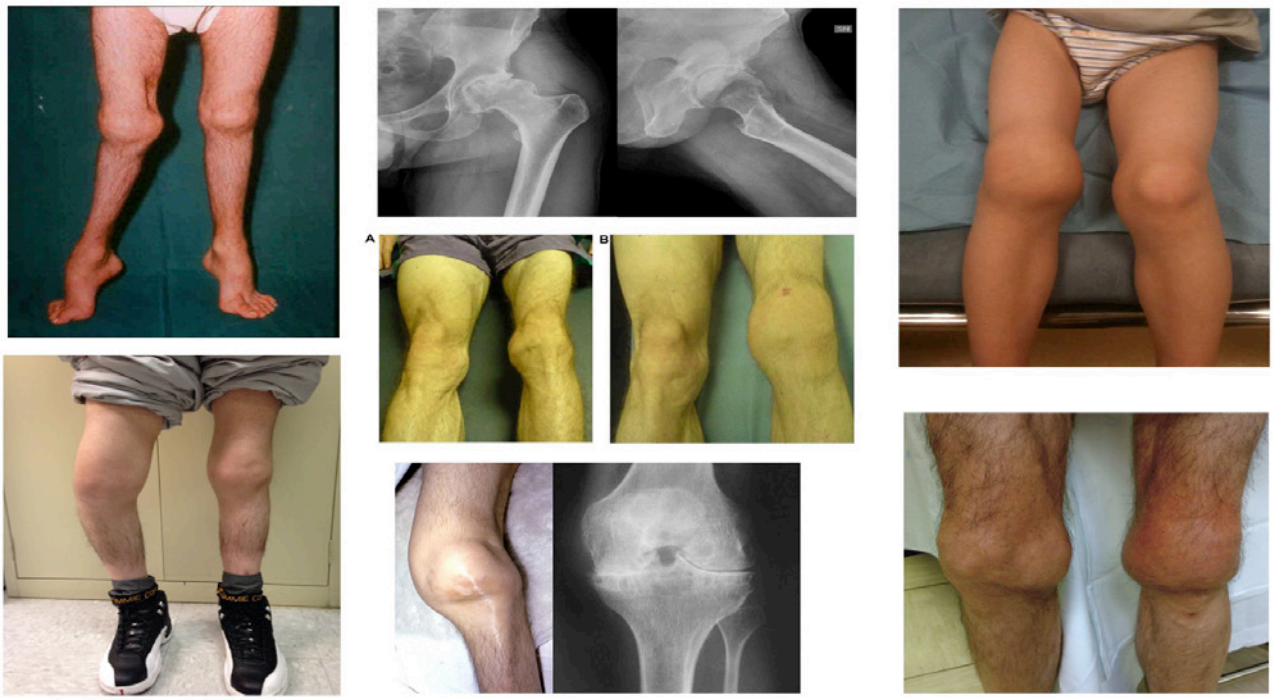
ARTROPATIA IN EMOFILIA



ARTROPATIA EMOFILICA DEFINIZIONE E SINTOMI

L'artropatia emofilica è una complicanza che si sviluppa in soggetti affetti da emofilia grave A o B in conseguenza al versamento ed accumulo ematico intra-articolare.

I sintomi negli stadi iniziali della malattia includono tumefazione, ridotto movimento e debolezza muscolare
Gli stadi più avanzati sono caratterizzati da una sinovite infiammatoria accompagnata da distruzione articolare, dolore e grave limitazione funzionale.

CAUSE INIZIALI DI ARTROPATIA: GLI EMARTRI

Negliemofilicigraviil 70-80% deisanguinamentisonoarticolari

Incidence of bleeding into different joints

- Knee: 45%
- Elbow: 30%
- Ankle: 15%
- Shoulder: 3%
- Wrist: 3%
- Hip: 2%
- Other: 2%

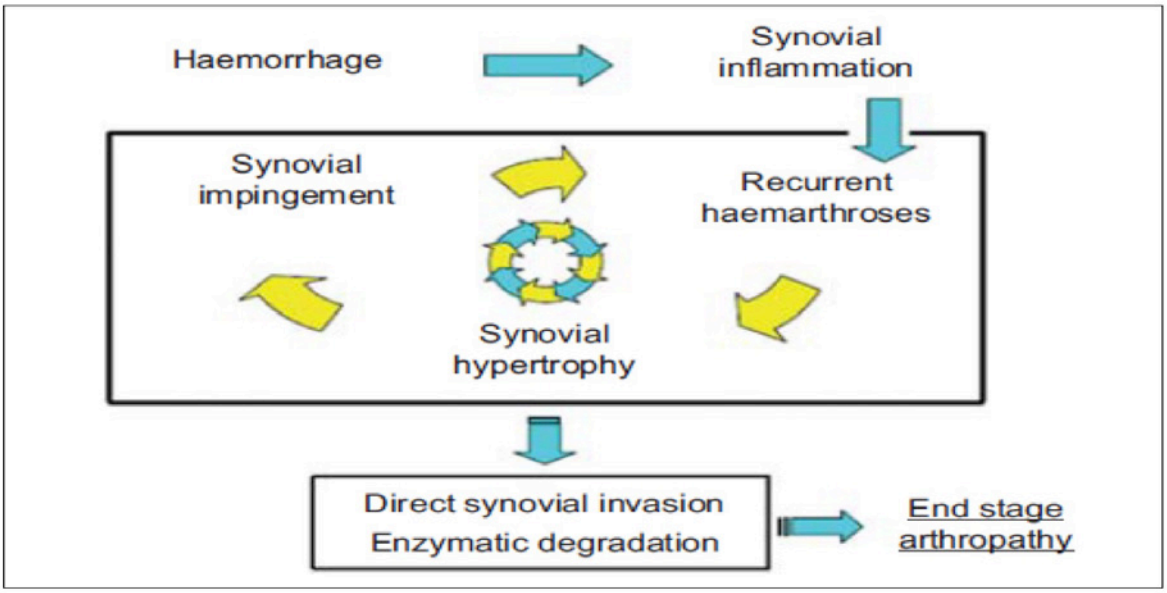
WFH Montreal 2005

CAUSE INIZIALI DI ARTROPATIA: GLI EMARTRI

Prime manifestazioni quando il bimbo inizia a gattonare e poi a camminare

- Gli episodi più frequenti si evidenziano nei bambini tra i 6 e 15 anni
- Dolore, rigidità e gonfiore sono i sintomi piùfrequenti
- Articolazionibersaglio (target joints)

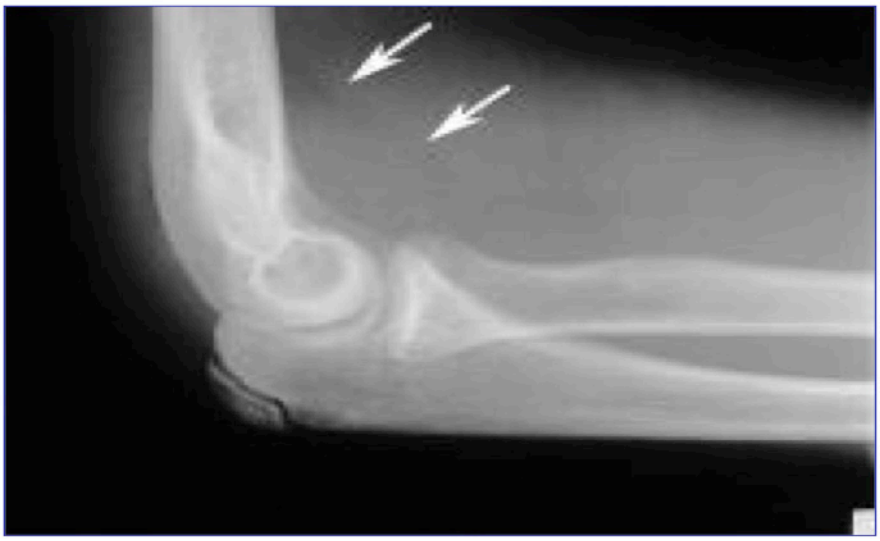
MECCANISMO DELL'ARTROPATIA



Knobe K, Berntorp E, J ofComorbidity 2011

EMARTROSI SUB-ACUTA

- Si sviluppa dop oripetut isanguinamenti
- Infiammazione delle sinovie
- Ipertrofia, iperplasia e aumento della vascolarità della membrana
- Emosiderosi: l'HB intraarticolare viene degradata, il ferro si deposita negli spazi intra-articolari

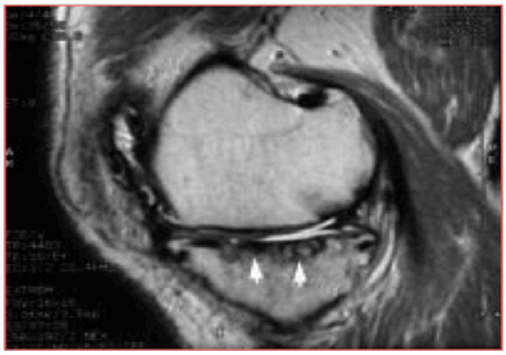


Esempio di emosiderosi in paziente emofilico

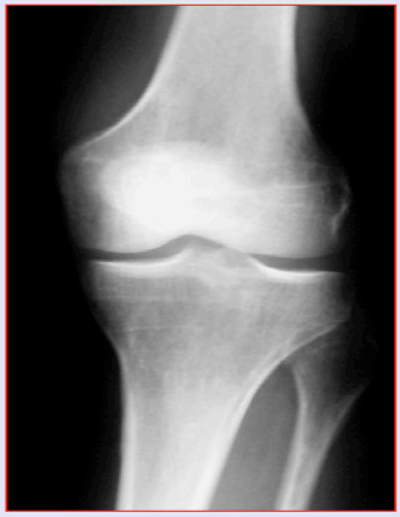
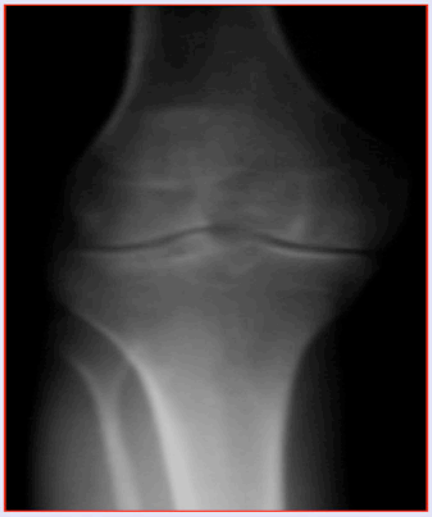
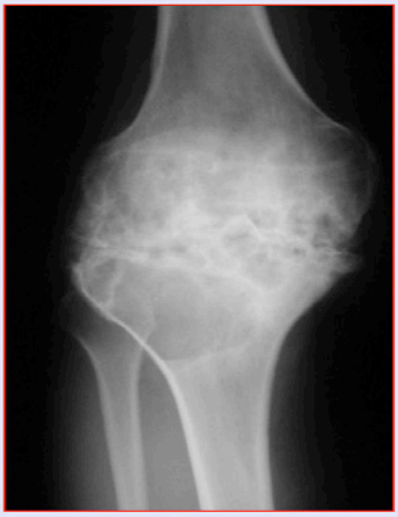
ARTROPATIA EMOFILICA CRONICA

- Progressivo danno alle articolazioni
- Progressiva distruzione della cartilagine articolare
- Riduzione degli spazi articolari
- Microfratture e formazioni di cisti nell'osso subcondrale
- Osteoporosi
- Andatura anchilosante

RMN: erosione cartilaginea e presenza di cisti subcondrali



ARTROPATIA EMOFILICA

PETTERSSON SCORE: Definizione

Strumento che si basa sulle radiografie di ginocchia, anche e caviglie del paziente a cui assegna un diverso punteggio ai diversi elementi considerati.

Lo score valuta per ogni articolazione interessata: osteoporosi, allargamento epifisi, irregolarità della superficie subcondrale, presenza di cisti subcondrali, ecc.

Il punteggio varia da 0 (assenza di artropatia) a 78 (deformità grave).

VALUTAZIONE DELL'ARTROPATIA MEDIANTE SCORES

Joint Scoring: Pettersson Score A Radiological Evaluation

Radiological Change	Finding	Score
Osteoporosis	Absent/Present	0/1
Enlargement of epiphysis	Absent/Present	0/1
Irregularity of subchondral surface	Absent/Slight/Pronounced	0/1/2
Narrowing of joint spaces	Absent/<50%/>50%	0/1/2
Subchondral cyst formation	Absent/1 cyst/>1 cyst	0/1/2
Erosions at joint margins	Absent/Present	0/1
Incongruence between joint surfaces	Absent/Slight/Pronounced	0/1/2
Deformity	Absent/Slight/Pronounced	0/1/2

Pettersson H, et al. *Clin Orthop Relat Res.* 1980;(149):153-159.

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PETTERSON SCORE: Limiti

Score lungo e complesso.

Molti elementi da valutare per ogni articolazione coinvolta.

Necessita di esami radiologici per la determinazione del punteggio (radiografie)

GILBERT SCORE: Definizione

Strumento che misura lo stato delle articolazione più colpite dall'artropatia emofilica (ginocchia, caviglie, gomiti), la loro struttura e compromissione funzionale.

È stato progettato principalmente per adulti e per bambini con artropatia confermata. Può essere utilizzato in caso di intervento chirurgico ortopedico o per valutare gli outcomes delle terapie fisioterapiche.

GILBERT SCORE

THE CLASSIFICATION RECOMMENDED BY THE ORTHOPEDIC ADVISORY COMMITTEE OF THE WORLD FEDERATION OF HEMOPHILIA

The clinical evaluation includes patient data, joint evaluation and physical evaluation as detailed below:

I. Patient Data
1. Age
2. Factor deficiency (VIII, IX, etc.)
3. Factor level
4. Inhibitor (Yes or No)
5. Mode of treatment
   O = No, or minimal transfusion therapy
   E = Episodic transfusion for most of all bleeding episodes
   M = Maintenance or prophylactic therapy
   (H) = Added after E or M indicates that the patient is on a homeself-transfusion program

Example: 16: VIII: <1:NO:E(H)
A 16-year-old patient, factor VIII deficient, with a level of less than 1%. He does not have an inhibitor and treats at home on an episodic basis.

II. *Joint Evaluation* **(of the nonbleeding joint)**

1. Pain	0-3
2. Bleeding	0-3
3. Physical examination	0-12
4. Radiologic evaluation	0-13

If the limb described requires an aid to ambulation, the following letters should be added at the end of the evaluation:
B = Brace or orthosis
C = Cane
CR = Crutches
WC = Wheelchair

PAIN
0: No pain
No functional deficit
No analgesic use (except with acute hemarthrosis)
1: Mild pain
Does not interfere with occupation nor with activities of daily living (ADL)
May require occasional non-narcotic analgesic
2: Moderate pain
Partial or occasional interference with occupation or ADL
Use of non-narcotic medications
May require occasional narcotics
3: Severe pain
Interferes with occupation or ADL
Requires frequent use of non-narcotic and narcotic medications

BLEEDING
This is measured by the number of minor and major hemarthroses *per year.*
0 = None
1 = No major, 1-3 minor
2 = 1-2 major or 4-6 minor
3 = 3 or more major or 7 or more minor

Guidelines

Minor	*Major*
Mild pain	Pain
Minimal swelling	Effusion
Minimal restrictions of motion	Limitation of motion
Resolves within 24hrs of treatment	Failure to respond within 24hrs

PHYSICAL EXAMINATION
This is based on an additive score of 0-12 with 0 being a normal join and 12 being most affected. An (5) is added after the number if a chronic synovitis is clinically diagnosed

Swelling	0 or 2→(5)
Muscle atrophy	0-1
Axial deformity	0-2
Crepitus on motion	0-1
Range of motion	0-2
Flexion contracture	0 or 2
Instability	0-2

Guidelines

Swelling:
0 = None
2 = Present
(5) = Added after score if chronic synovitis is present

Muscle atrophy:
0 = None or minimal (<1 cm)
1 = Present

Axial deformity (measured only at knee or ankle):
Knee
0 = Normal = 0-7° valgus
1 = 8-15° valgus or 0-5° varus
2 = >15° valgus or >5° varus
Ankle
0 = No deformity
1 = Up to 10° valgus or up to 5° varus
2 = >10° valgus or >5° varus

Crepitus on motion:
0 = None
1 = Present

Range of motion:
0 = Loss of 10% of total full range of motion (FROM)
1 = Loss of 10-33 1/3% of total FROM
2 = Loss of >33 1/3% of total FROM

Flexion contracture:
Measured only at hip, knee, or ankle
0 = <15° FFC (fixed flexion contracture)
2 = 15° or greater FFC at hip or knee or equines at ankle

Instability:
0 = None
1 = Noted on examination but neither interferes with function nor requires bracing
2 = Instability that creates a functional deficit or requires bracing

GILBERT SCORE: Limiti

Richiede tempo per essere completato.

Potrebbe non essere appropriato per i bambini più piccoli poiché i normali cambiamenti osteo-articolari dovuti allo sviluppo potrebbero essere valutati come anormali.

Potrebbe non essere appropriato per le persone con artropatia lieve, trattate da sempre in profilassi, poiché potrebbe risultare poco sensibile a lievi alterazioni articolari.

HAEMOPHILIA JOINT HEALTH SCORE

La scala HJHS misura la salute articolare delle strutture più frequentemente colpite da emorragia in pazienti affetti da emofilia: le ginocchia, le caviglie e i gomiti.

HJHS era stato progettato principalmente per i bambini con emofilia di età compresa tra 4-18 anni con compromissione articolare lieve (ad esempio trattati con profilassi).

Il HJHS è uno strumento di valutazione sensibile ai primi lievi segni di danno articolare.

Permette un monitoraggio dei cambiamenti articolari nel tempo e la valutazione dell'efficacia dei regimi di trattamento in bambini sottoposti a terapia, sia profilattica che on-demand.

HAEMOPHILIA JOINT HEALTH SCORE

Hemophilia Joint Health Score 2.1 - Summary Score Sheet

	Left Elbow	Right Elbow	Left Knee	Right Knee	Left Ankle	Right Ankle
Swelling	☐ NE	☐ NE	☐ NE	☐ NE	☐ NE	☐ NE
Duration (swelling)	☐ NE	☐ NE	☐ NE	☐ NE	☐ NE	☐ NE
Muscle Atrophy	☐ NE	☐ NE	☐ NE	☐ NE	☐ NE	☐ NE
Crepitus on motion	☐ NE	☐ NE	☐ NE	☐ NE	☐ NE	☐ NE
Flexion Loss	☐ NE	☐ NE	☐ NE	☐ NE	☐ NE	☐ NE
Extension Loss	☐ NE	☐ NE	☐ NE	☐ NE	☐ NE	☐ NE
Joint Pain	☐ NE	☐ NE	☐ NE	☐ NE	☐ NE	☐ NE
Strength	☐ NE	☐ NE	☐ NE	☐ NE	☐ NE	☐ NE
Joint Total						

Sum of Joint Totals +

Global Gait Score

(☐ NE included in Gait items)

HJHS Total Score =

NE = Non-Evaluable

Swelling
0 = No swelling
1 = Mild
2 = Moderate
3 = Severe

Duration
0 = No swelling or < 6 months
1 = ≥ 6 months

Muscle Atrophy
0 = None
1 = Mild
2 = Severe

Joint Pain
0 = No pain through active range of motion
1 = No pain through active range; only pain on gentle overpressure or palpation
2 = Pain through active range

Crepitus on Motion
0 = None
1 = Mild
2 = Severe

Flexion Loss
0 = < 5°
1 = 5° - 10°
2 = 11° - 20°
3 = > 20°

Extension loss
(from hyperextension)
0 = < 5°
1 = 5° - 10°
2 = 11°- 20°
3 = > 20°

Strength (Using The Daniels & Worthingham's scale)
Within available ROM
0 = Holds test position against gravity with maximum resistance (gr.5)
1 = Holds test position against gravity with moderate resistance (but breaks with maximal resistance) (gr.4)
2 = Holds test position with minimal resistance (gr. 3+), or holds test position against gravity (gr.3)
3 = Able to partially complete ROM against gravity (gr.3-/2+), or able to move through ROM gravity eliminated (gr.2), or through partial ROM gravity eliminated (gr.2-)
4 = Trace (gr.1) or no muscle contraction (gr.0)
NE = Non-evaluable

Global Gait (walking, stairs, running, hopping on 1 leg)
0 = All skills are within normal limits
1 = One skill is not within normal limits
2 = Two skills are not within normal limits
3 = Three skills are not within normal limits
4 = No skills are within normal limits
NE = Non-evaluable

HAEMOPHILIA JOINT HEALTH SCORE

Limiti:

a) HJHS richiede molto tempo per essere somministrato

b) non è ancora stato adeguatamente studiato per l'uso negli adulti e nelle patologie ad interesse articolare più invalidanti.

L'ESPERIENZA SVEDESE

Età attuale	3-6 anni	7-12 anni	13-17 anni	18-23 anni	24-32 anni
No. pazienti	6	9	20	10	15
Età di inizio (anni)	1.1 (1-1.5)	1.2 (0.5-2)	2.6 (1-4.5)	4.9 (3-7)	7.0 (3-13)
Emorragie articolari (per anno)	0.1 (0.0-6)	0.1 (0.0-4)	3 (0.1-16.6)	5.6 (0.5-14)	5.0 (1.6-16)
Dose Totale FVIII/FIX per kg/ anno (x 103)	4.3 (3.0-7.0)	4.0-7.4 (1.7-9.0)	1.5-4.9 (0.8-6.6)	1.2-3.8 (0.5-5)	0.4-2.6 (0.2-6)
Livello pre-infusione VIII:C/ IX:C	2(1-5)	1 (1-4)	<1-3	1-2.5	<1-2.5
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)
Giorni di lavoro/ scuola persi (per anno)	0	0	0.9 (0.6-7)	2.8 (0-9.8)	5.8 (1-20)

Nilsson et al. J Intern Med 1992

BLEEDING: PROFILASSI vs ON-DEMAND

Il trattamento profilattico precoce riduce il sanguinamento articolare.

Present Age	3–12 Years	13–20 Years	21–26 Years	27–35 Years
Number of patients	21 (18A, 3B)	19 (16A, 3B)	10 (9A, 1B)	15 (13A, 2B)
Age at start of treatment/years	1–2	2.5 (1–4.5)	4.9 (3–7)	7.0 (3–13)
Joint bleeds/year (range)	0.2 (0–1.2)	2.6 (0.2–17)	5.6 (0.5–14)	5.0 (1.6–16)
Total annual dose of factor VIII/IX p log U × 10^3 (range)	5.9 (4.1–9.8)	1.6 → 5.4 (0.8–7.2)	1.2 → 2.7 (0.5–6.5)	0.4 → 3.3 (0.2–5.9)
VIII:C/IX-C before Infusion, IU/dL	2 (1–5)	< 1–3	< 1–2.5	< 1–2.5
Orthopedic joint score (range)	0	1.2 (0–7)	2.9 (0–7)	6.6 (0–15)
Radiological joint score (range)	0	4.8 (0–22)	14.2 (0–22)	20.6 (0–41)
Annual absence from school/work, days (range)	NA	0.9 (0.6–7)	2.8 (0–9.8)	5.8 (1–20)

Aledort , Semin Thromb Haemost, 2003

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.

Journal of Thrombosis and Haemostasis, **9**: 700–710 DOI: 10.1111/j.1538-7836.2011.04214.x

ORIGINAL ARTICLE

A randomized clinical trial of prophylaxis in children with hemophilia A (the ESPRIT Study)

A. GRINGERI,* B. LUNDIN,† S. VON MACKENSEN,*‡ L. MANTOVANI,§ P. M. MANNUCCI*¶ and THE ESPRIT STUDY GROUP[1]

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Table 1 Baseline demographic characteristics of trial groups

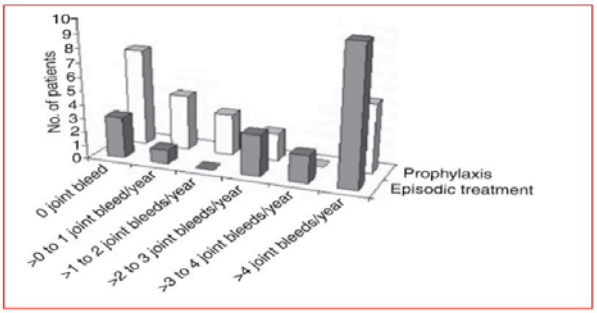
Characteristic	Prophylaxis (n = 21)	Episodic treatment (n = 19)	P value
Age, months			
Mean ± SD	49.7 ± 26.9	48.8 ± 21.2	ns
Median (min–max)	50 (10–84)	48 (14–84)	
Age groups, n (%)			
≤36 months	8 (38)	7 (38)	ns
37–60 months	6 (29)	6 (32)	
>60 months	7 (33)	6 (32)	
Age at diagnosis, months			
Mean ± SD	5.7 ± 6.2	8.8 ± 10.1	ns
Median (min–max)	6 (0–23)	6 (0–32)	
Body mass index, kg m^{-2}			
Mean ± SD	16.4 ± 0.8	16.4 ± 0.7	ns
Median (min–max)	16.2 (15.5–18.2)	15.5 (15.5–17.9)	

SD, standard deviation.
ns, not significant.

STUDIO ESPRIT

Variable	Prophylaxis (n = 21)	Episodic Treatment (n = 19)	P value
No. of months in randomization arm			
Mean	46.2	51.8	ns
Median (min–max)	54.5	58.6	
No. of patient years	81	82	
Total bleeding events per patient			
Mean	5.0	24.9	< 0.01
Median (min–max)	1	7.5	
No. of events per patient per month	0.11	0.48	
No. of hemarthroses per patient			
Mean	2.48	12.42	< 0.01
Median (min–max)	0	4	
No. of events per patient per month	0.05	0.24	
Radiographic findings			
Joint damage, no. (%)	0	5	ns
No joint damage, no. (%)	21	14	

ns, not significant.



Gringeri al. J Thromb Haemost 2011

PROFILASSI IN EMOFILIA

Table 1. Baseline Demographic and Clinical Characteristics of All Randomized Participants.

Characteristic	Prophylaxis (N=32)	Enhanced Episodic Therapy (N=33)	P Value
Mean age (yr)	1.6	1.6	0.78
Race or ethnic group — no. (%)*			0.33
White	24 (75)	25 (76)	
Black	0	3 (9)	
Hispanic	4 (13)	4 (12)	
Asian or Pacific Islander	1 (3)	1 (3)	
American Indian or Alaskan native	1 (3)	0	
Other	2 (6)	0	
Educational level of parent or guardian — no. (%)			0.06
≤12 yr	20 (63)	13 (39)	
>12 yr	12 (37)	20 (61)	
First index-joint hemorrhage before enrollment — no. (%)			0.17
Yes	18 (56)	13 (39)	
No	14 (44)	20 (61)	
No. of previous index-joint hemorrhages			0.17
Mean	1.0	0.6	
Range	0–5	0–3	
No. of previous total hemorrhages			0.74
Mean	6.2	6.8	
Range	0–35	0–32	

* Race and ethnic group were reported by the parent or guardian of each child.

Table 2. Outcome Data.*

Variable	Prophylaxis (N=32)	Enhanced Episodic Therapy (N=33)	P Value
MRI findings			
No. of participants with primary outcome data	27	29	0.73
Joint damage — no. (%)	2 (7)	13 (45)	0.002
No joint damage — no. (%)	25 (93)	16 (55)	
Radiographic findings			
No. of participants with primary outcome data	28	27	0.73
Joint damage — no. (%)	1 (4)	5 (19)	0.10
No joint damage — no. (%)	27 (96)	22 (81)	
No. of days in study			
Mean	1,497	1,490	0.95
Total	47,895	49,179	
Reported no. of factor VIII infusions			
Mean	653±246	187±100	<0.001
Total	20,896	6,176	
Reported no. of factor VIII units infused			
Mean	352,793±150,454	113,237±65,494	<0.001
Total	11,289,372	3,736,807	
Joint hemorrhages (no./participant/yr)			
Mean	0.63±1.35	4.89±3.57	<0.001
Median	0.20	4.35	
Total hemorrhages (no./participant/yr)			
Mean	3.27±6.24	17.69±9.25	<0.001
Median	1.15	17.13	

* Plus–minus values are means ±SD. The data on MRI and radiographic findings include interim-analysis data for children who were removed from the study because of early joint failure.

Manco-Johnson M, NEJM 2007

PROFILASSI SECONDARIA IN EMOFILIA

	Prophylaxis		On Demand		P between treatment cohorts
	Age 12–25 years (n=14)	Age 26–55 years (n=13)	Age 12–25 years (n=11)	Age 26–55 years (n=15)	
Follow-up duration, years Median (range)	5.4 (4.0–6.0)	5.7 (4.0–6.0)	5.7 (5.0–6.0)	5.3 (0.5–6.0)	
Joint bleeding episodes Mean^ (SD) Median^ (range)	2.0 (2.0) 1.1 (0.2–5.6)	3.4 (4.6) 2.0 (0.0–17.6)	16.6 (12.4) 14.2 (2.4–48.6)	13.7 (11.2) 9.2 (1.6–40.6)	0.0043†
Annualised bleeding rate* Observed Estimated by model (95% CI)	1.97 1.92 (1.2–3.2)	2.46 2.46 (1.5–4.1)	16.80 16.05 (10.2–25.3)	16.71 18.04 (12.5–26.1)	
Total bleeding episodes Mean (SD) Median (range)	2.6 (2.2) 2.1 (0.2–6.8)	4.5 (7.1) 2.2 (0.0–27.4)	19.5 (15.0) 15.6 (6.0–60.8)	17.7 (11.7) 15.0 (2.2–47.6)	0.0048†
Annualised bleeding rate* Observed Estimated by model (95% CI)	2.54 2.47 (1.6–3.8)	2.95 2.95 (1.8–4.7)	19.77 19.14 (12.2–30.1)	21.49 22.40 (16.3–30.8)	
Target joints¤ Number of patients (%) Mean number per patient (total number)	2 (14.3) 0.14 (2)	5 (38.5) 0.77 (10)	9 (81.8) 1.64 (18)	12 (80.0) 1.93 (29)	<0.001**
Orthopaedic Joint Score (pain + physical examination), mean (SD) Baseline Last evaluation‡ Change last evaluation vs baseline	3.2 (3.3) 3.0 (2.4) −0.2 (3.4)	13.3 (15.4) 10.1 (12.5) −3.2 (9.7)	5.4 (3.0) 8. 8 (4.4) +3.6 (4.8)	17.1 (10.3) 21.5 (12.8) +4.4 (6.2)	0.0019§
Pettersson score, mean (SD)‖ Baseline Last evaluation¶ Change last evaluation vs baseline	4.3 (4.5) 5.5 (4.9) +1.2 (1.6)	20.0 (18.9) 22.2 (18.5) +2.2 (2.8)	3.3 (4.9) 5.7 (6.7) +2.3 (2.1)	22.2 (15.1) 35.0 (17.2) +12.8 (12.3)	0.0177§
Total average consumption rFVIII, IU/kg/year Mean (SD) Median Range	3795.8 (1030.7) 3998.0 887.8–4858.0	3664.5 (763.8) 3844.4 2259.3–5261.2	1367.7 (1330.1) 786.4 432.3–4305.1	2004.2 (1321.1) 1651.3 211.8–4562.3	<0.0001#
Mean number of days of everyday activities lost/ patient-/caregiver-year	10.6	13.8	43.0	35.6	<0.001**

Tagliaferri et. al., Thromb Haemost, 2015

ATTIVITA' FISICA: PROFILASSI vs A DOMANDA

	Always prophylaxis ($N = 64$)	Always on-demand ($N = 36$)	On-demand as child, switched to prophylaxis ($N = 74$)	P-value
General activity				
Superior	3	3	5	0.024*, <0.028†
Equal	29	17	11	
Lower	58	44	63	
Inactive	10	36	20	
Walking speed				
Faster	8	3	7	<0.001*, <0.001†
Equal	42	14	1	
Slower	32	54	63	
Much slower	18	29	29	
Walking distance not limited	41	14	7	<0.001*, <0.001†

*Always prophylaxis vs both groups on –demand

† Always prophylaxis vs on-demand switched to prophylaxis

Mondorf et al., Haemophilia 2013

ALTRE ATTIVITA' : PROFILASSI vs A DOMANDA

	Always prophylaxis ($N = 64$)	Always on-demand ($N = 36$)	On-demand as child, switched to prophylaxis ($N = 74$)	P-value
Kindergarten	64	50	49	n.s.*, n.s.†
School sports				
Always	14	0	0	<0.001*, 0.001†
Mostly	23	11	12	
Seldom	16	17	18	
Never	47	72	70	
Further education				
University	50	33	26	0.047*, n.s.†
Apprenticeship	50	67	74	
None	0	0	0	

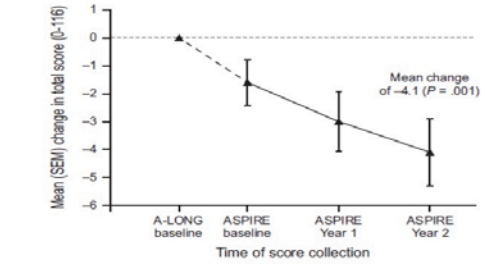
*Always prophylaxis vs both groups on –demand

† Always prophylaxis vs on-demand switched to prophylaxis

Mondorf et al., Haemophilia 2013

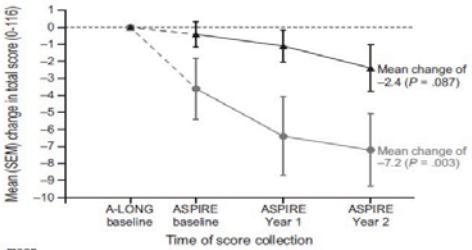
rFVIIIFc e score articolari (mHJHS)

Un miglioramento continuo nel tempo dello score articolare mHJHS (tutti i soggetti)



	A-LONG baseline	ASPIRE baseline	ASPIRE Year 1	ASPIRE Year 2
Total score, mean (n = 47)	23.4	21.9	20.4	19.3

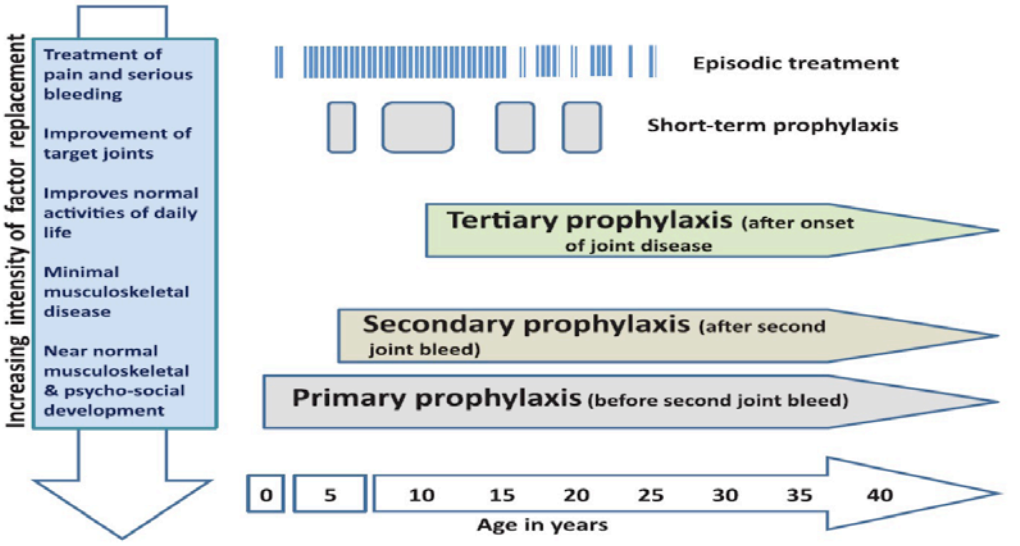
Un miglioramento continuo nel tempo dello score articolare mHJHS sia in pazienti in profilassi che on-demand



	A-LONG baseline	ASPIRE baseline	ASPIRE Year 1	ASPIRE Year 2
Total score, mean				
▲ Prophylaxis (n = 30)	21.0	20.6	19.9	18.6
● Episodic (on demand; n = 17)	27.6	24.0	21.4	20.4

Oldemburget al., Haemophilia 2018

PROFILASSI IN EMOFILIA



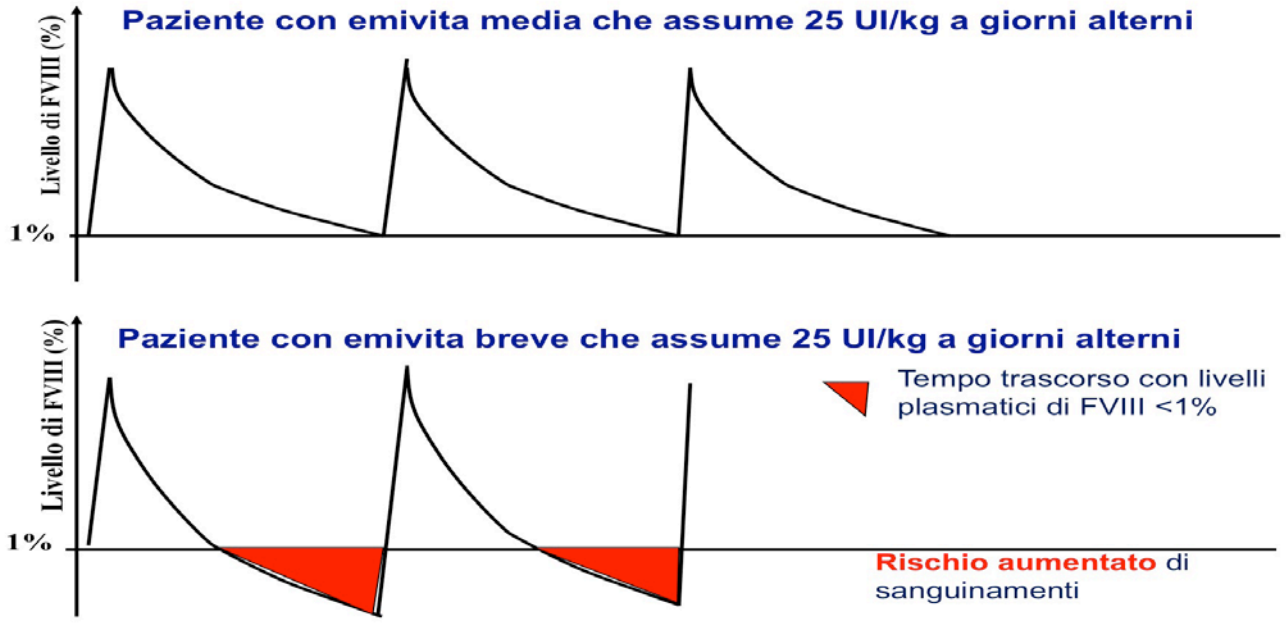
Adapted from Blood Transfus 2008 Sep;6 Suppl 2:s4-11

PROFILASSI: MODALITA'

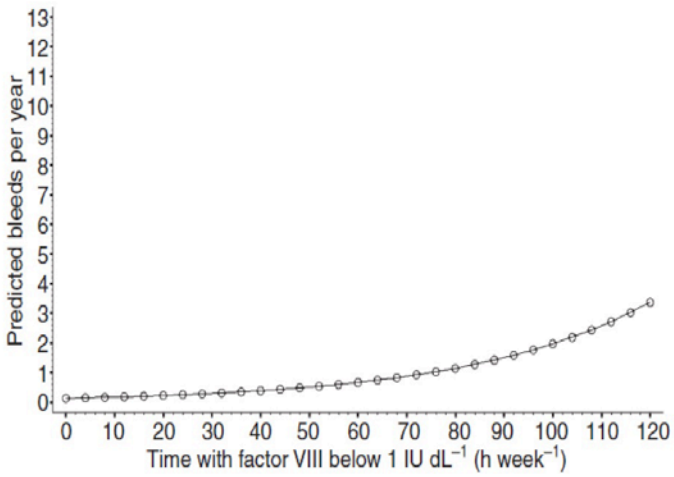
Prophylactic dosing regimen	Dose	Dosing frequency	Dosing adjustments
Swedish (Malmö) high-dose protocol (24, 50, 51)	25–40 IU/kg	3 times weekly or every other day	Dosing adjusted to maintain FVIII levels >1 %
Utrecht (intermediate-dose) protocol (2, 52)	15–30 IU/kg	2 or 3 times weekly	Dosing adjusted based on patient's bleeding pattern
Canadian dose-escalation protocol (27)	50 IU/kg	Once weekly	Escalate to 30 IU/kg twice weekly or 25 IU/kg on alternate days based on patient's bleeding frequency

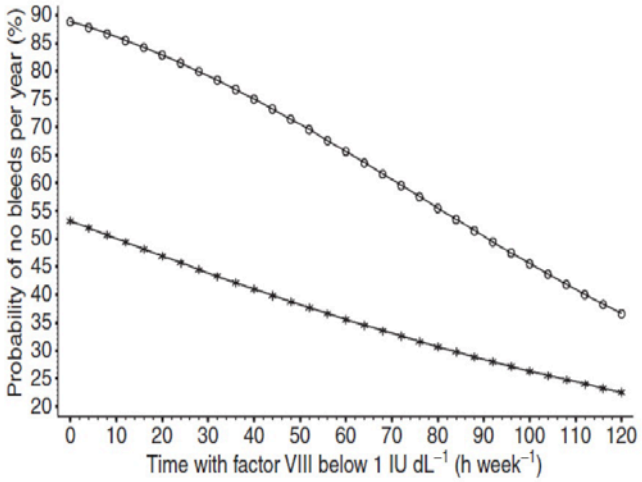
Ljung R. et al. Thromb Haemost 2016

LIMITI DELLA PROFILASSI STANDARD



INSORGENZA DI SANGUINAMENTI E LIVELLI DI FVIII < 1%





Collins PW et al. J Thromb Haemost 2009;7:413-20

L'EVOLUZIONE DELLA PROFILASSI IN EMOFILIA

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Emicizumab Prophylaxis in Patients Who Have Hemophilia A without Inhibitors

J. Mahlangu, J. Oldenburg, I. Paz-Priel, C. Negrier, M. Niggli, M.E. Mancuso, C. Schmitt, V. Jiménez-Yuste, C. Kempton, C. Dhalluin, M.U. Callaghan, W. Bujan, M. Shima, J.I. Adamkewicz, E. Asikanius, G.G. Levy, and R. Kruse-Jarres

Table 2. Treated Bleeding Events in Participants Receiving Emicizumab Prophylaxis (Group D), as Compared with Events in the Same Participants during Prophylactic Factor VIII Treatment Previously in the Noninterventional Study.*

Variable	Group D in Current Trial: Emicizumab Prophylaxis (N=48)	Noninterventional Study: Factor VIII Prophylaxis (N=48)
Median duration of efficacy period (range) — wk†	33.7 (20.1–48.6)	30.1 (5.0–45.1)
Annualized rate of bleeding events, model-based (95% CI)‡	1.5 (1.0–2.3)	4.8 (3.2–7.1)
Rate ratio vs. control (95% CI)	0.32 (0.20–0.51)	—
Percent difference vs. control	−68§	—
Median annualized rate of bleeding events (IQR)	0.0 (0.0–2.1)	1.8 (0.0–7.6)
Percent of participants with 0 bleeding events (95% CI)	54 (39–69)	40 (26–55)
Percent of participants with 0–3 bleeding events (95% CI)	92 (80–98)	73 (58–85)

GRAZIE PER L'ATTENZIONE!