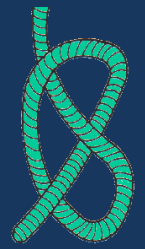


LA GESTIONE *GLOBALE* DEL PAZIENTE EMOFILICO

Giovanni Di Minno
AICE

Current treatment of bleeding disorders

Major inherited deficiencies of coagulation factors

Deficient factor (disease)	Incidence	Heritability	Gene (chromosome)	Replacement preparation(s)
von Willebrand Factor (von Willebrand disease)	1:5000	Autosomal, dominant	12	Plasma-derived concentrates, purified recombinant factor concentrates
Factor VIII (hemophilia A)	1:10,000	X-linked, recessive	X	Plasma-derived concentrates; purified recombinant factor concentrates
Factor IX (hemophilia B)	1:60,000	X-linked, recessive	X	Plasma-derived concentrates; purified recombinant factor concentrates
Factor VII	1:500,000	Autosomal, recessive	13	Plasma-derived concentrates; purified recombinant factor concentrate
Factor XI	1:1,000,000	Autosomal, recessive	4	Fresh frozen plasma; plasma-derived concentrate
Factor XIII	1:1,000,000	Autosomal, recessive	6 (sub. A) 1 (sub. B)	Fresh frozen plasma Plasma-derived concentrate; purified recombinant factor concentrate
Factor X	1:1,000,000	Autosomal, recessive	13	Plasma-derived prothrombin complex concentrates; plasma-derived concentrate
Fibrinogen (afibrinogenemia)	1:1,000,000	Autosomal, recessive	4	Plasma-derived concentrates
Factor V (parahemophilia)	1:1,000,000	Autosomal, recessive	1	Fresh frozen plasma
Factor II	1:2,000,000	Autosomal, recessive	11	Plasma-derived prothrombin complex concentrates

Life expectancy for patients with hemophilia

- Life expectancy for patients with hemophilia has improved as management strategies have improved
  - Italy
    - Life expectancy 71.2 years for 2000–2007 vs. 64.0 years for 1990–1997[1]
  - USA
    - Median age of death for non-HIV-infected patients with hemophilia A 72 years between 1995 and 1997[2]
  - The Netherlands
    - Life expectancy 72 years between 1992 and 2001[3]*

HIV = human immunodeficiency virus
*After exclusion of virus-related deaths
1. Tagliaferri A, et al. Haemophilia 2010;16:437-46; 2. Chorba TL, et al. Am J Hematol 2001;66:229-40;
3. Plug I, et al. J Thromb Haemost 2006;4:510-6.

“Comprehensive Care Approach”

- The Comprehensive Care Approach (in keeping with the European Principles of Haemophilia Care^) guarantees to Patients improvements in health care in terms of:
  - ✓ Survival
  - ✓ Hospitalizations, visits
  - ✓ Absenteeism form work and school
  - ✓ Cost of care
  - ✓ Damage of the joint

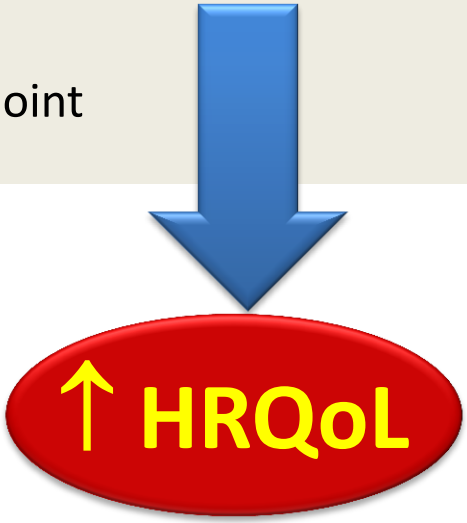


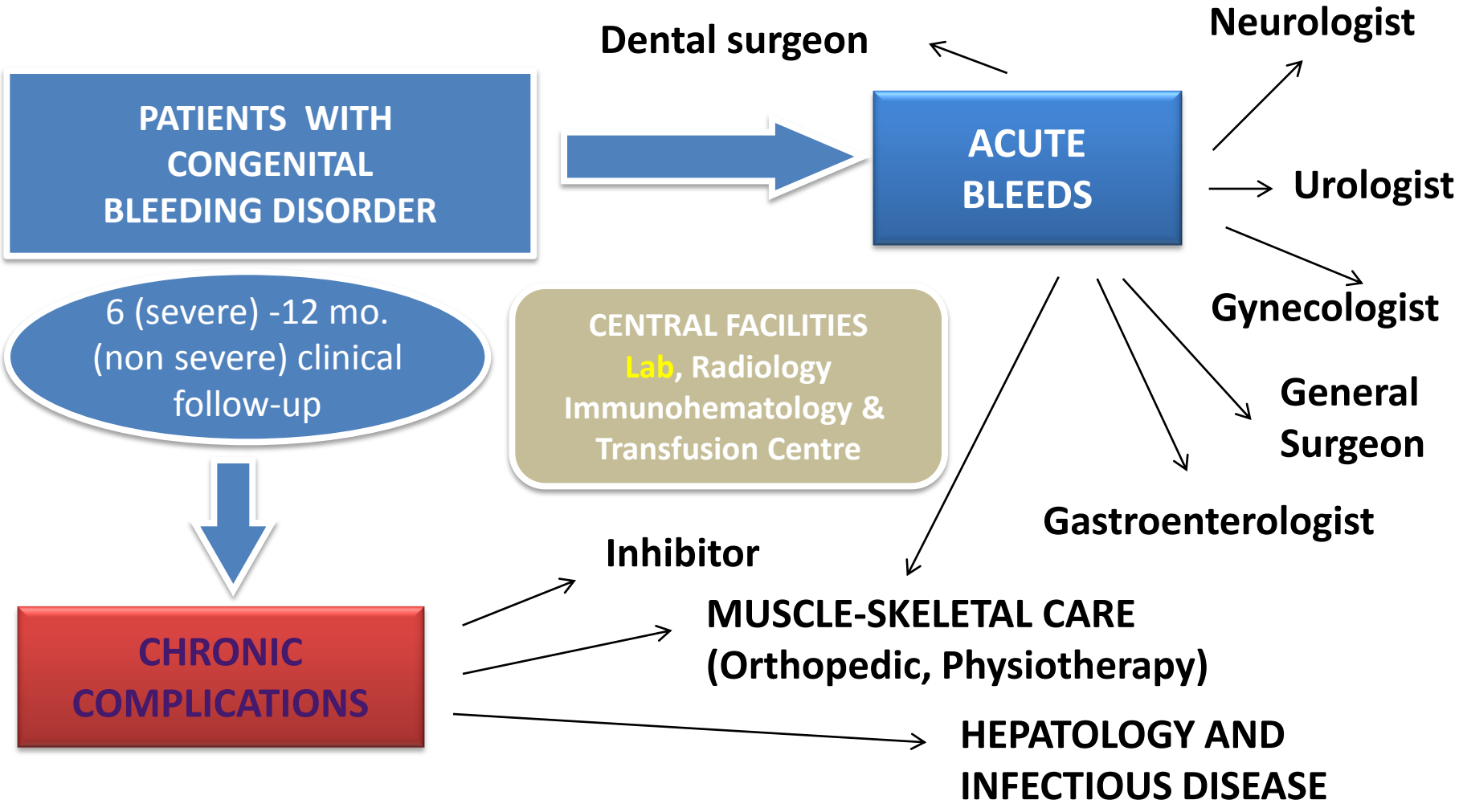
Table 1. Parameters studied to describe outcome of centralized haemophilia care.

Parameters studied		Evidence
Determinants of care	Clotting factor use (GNP)	
	Centralized care (HTC/CCC)	
	Home treatment	
Outcome parameters	Survival	+++
	Short term: costs	+
	Visits, hospital admission	++
	Unemployment	++
	Long term: joint status	No data
	Disability	No data

HTC, Haemophilia Treatment Centre; CCC, Comprehensive Care Centre.

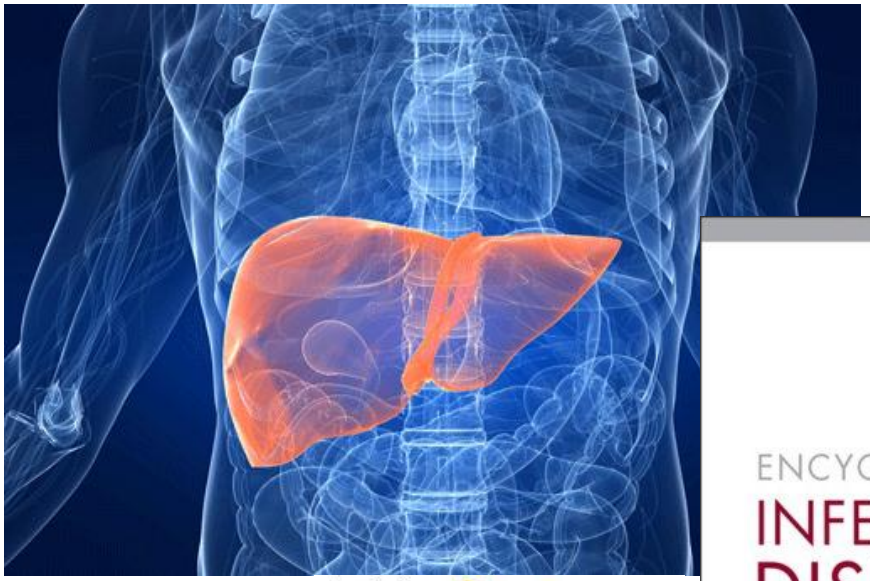
^Colvin et al, Haemophilia, 2008

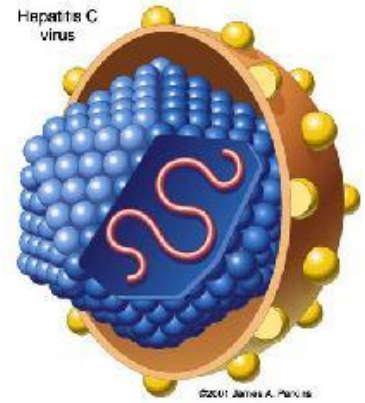
Comprehensive Care
History (1990s): the needs



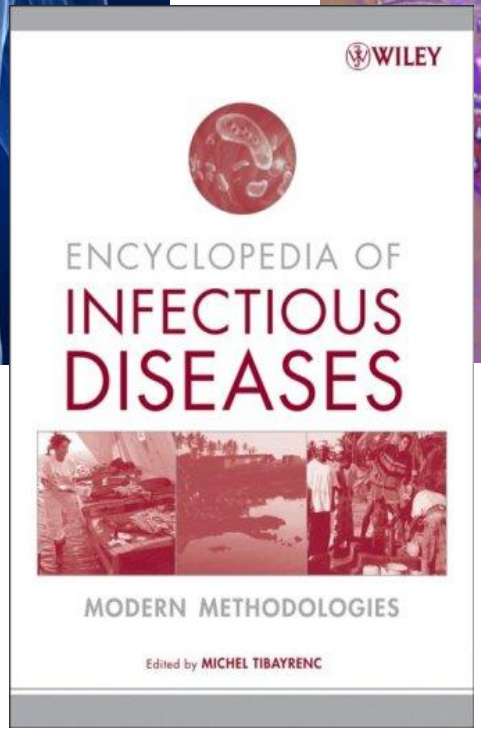
Comprehensive Care
History (1980-1990s): the core

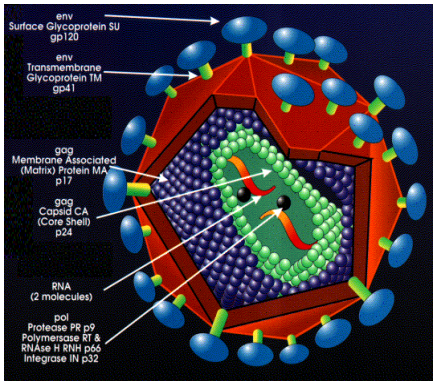
Hepatologic support





HIV Infection





Comprehensive Care
the 2000's

Hepatology care

- Large-scale implementation of combined antiviral treatment for HCV patients
- HCV patients with advanced disease: HCC screen and evaluation for liver transplantation (OLT)
- *Non invasive assessment of liver fibrosis (biomarkers, transient elastography)*

HIV patient treatment and care

- Implementation and individualization of HAART

Comprehensive Care

History (late 90's): the core

Dental surgery
when needed

Sporadically:
Conservative care
Parodontology

Regional Reference Centres for Coagulation Disorders
the 2000's

Comprehensive care activites

- Improvement and extension of specialty care, development and training of teams
- Organization for improvement and regulation of home treatment
- **Diffusion of secondary prophylaxis, particularly in young-adults**
- **Genetic database**

Regional Reference Centres for Coagulation Disorders Home treatment

Campania Region

2006, March: Regulation of Home Treatment for patients With bleeding disorders approved *(DGRC 288, 04.03.2006)*

2007, June: 1st Course for Home Treatment

Regional Reference Centres for Coagulation Disorders
the 2000's

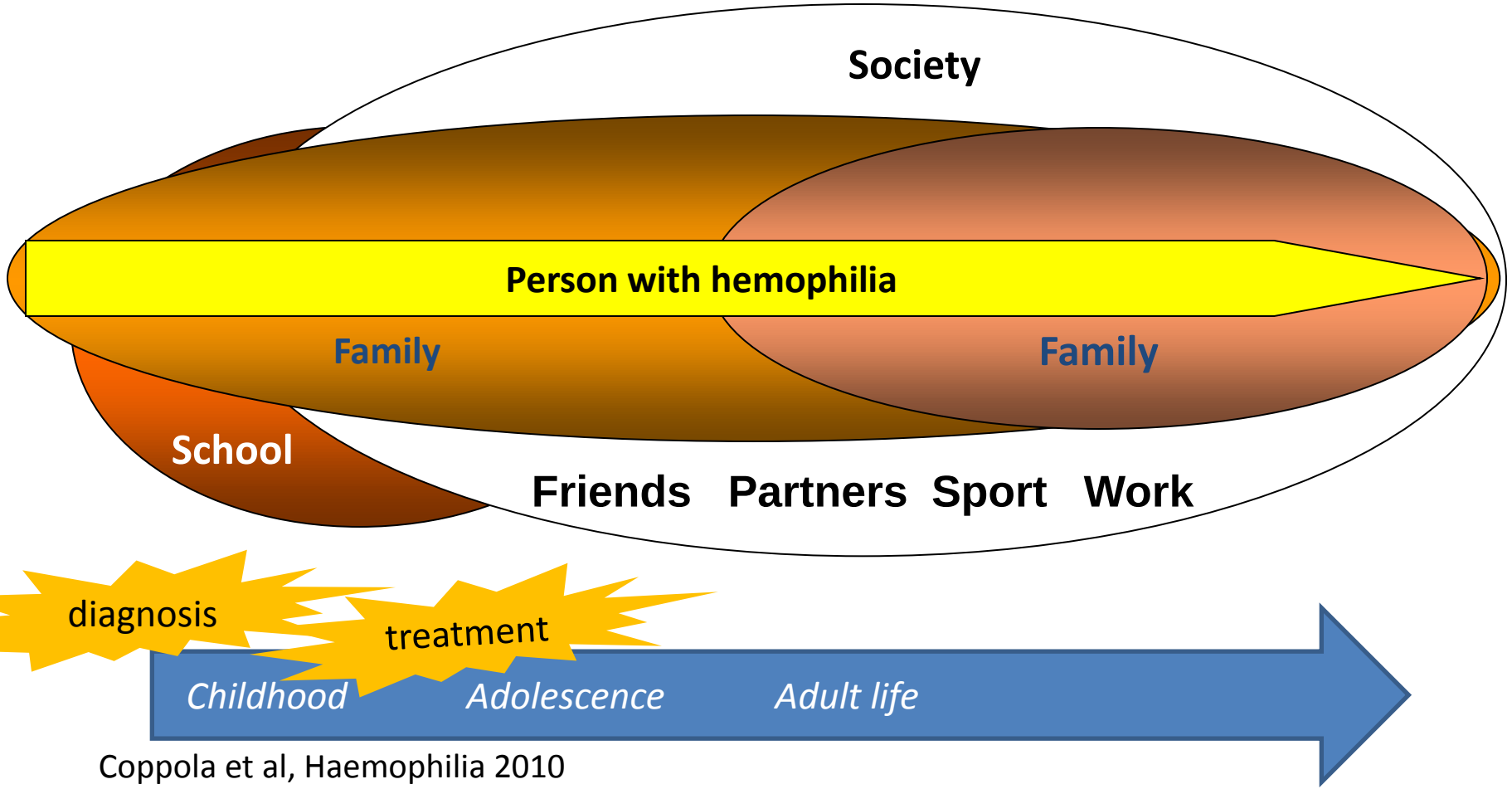
- All severe hemophilia A and B patients genotyped
  - **Genetic counseling, carrier identification and timely pre-natal diagnosis**
  - Genotype-phenotype studies
  - Risk of inhibitor development (and ITI failure?)
  - **Contribution to National databases and registries**

Psychological Support Program

- **Talk with your patient**
  - **Hemophilia and its treatment have a strong psychological impact on patients and their family.**
  - ***Prophylaxis is the standard of care in children and is increasingly prescribed in adults.***
  - **Patient, particularly in some phases of life, may be reluctant to multiple weekly injections, thus the adherence to therapy may be hampered.**
  - **Monitoring patients' sense of well-being, measuring HRQoL by validated instruments for recognizing psychological needs.**

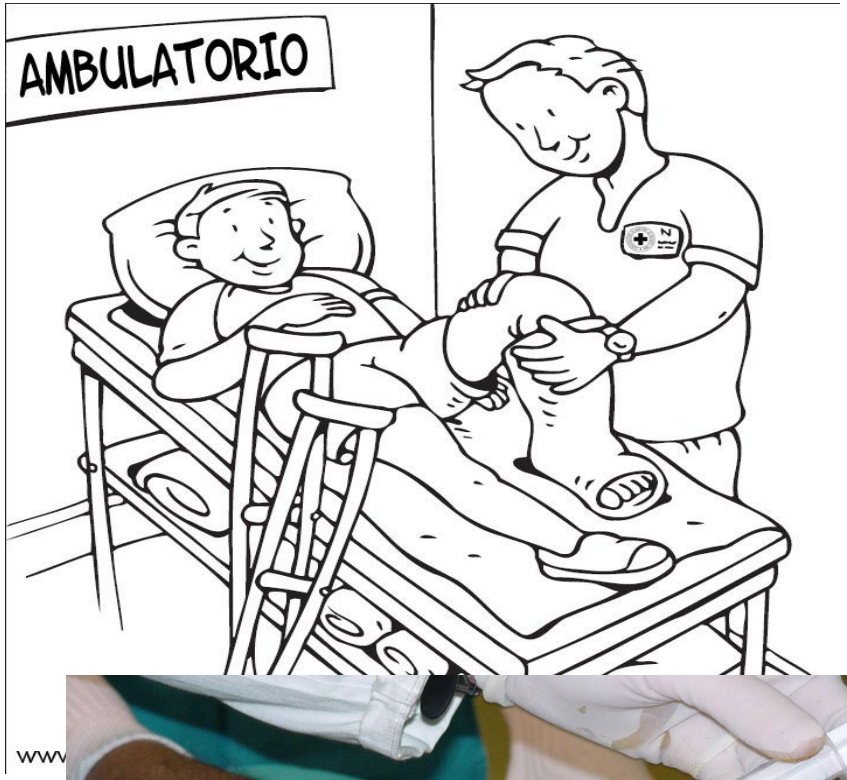
Psychological support

- Confronting the psychological burden of hemophilia throughout the life cycle



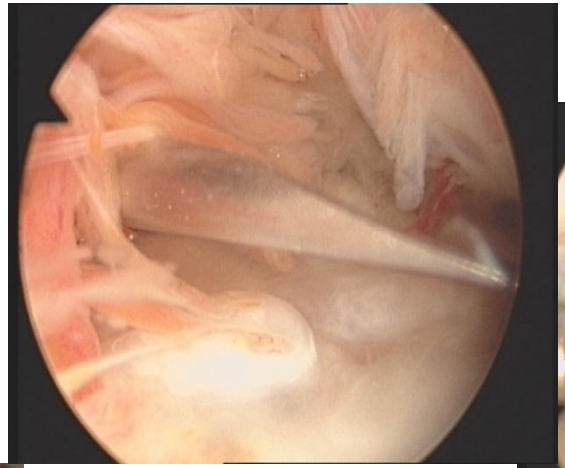
Coppola et al, Haemophilia 2010

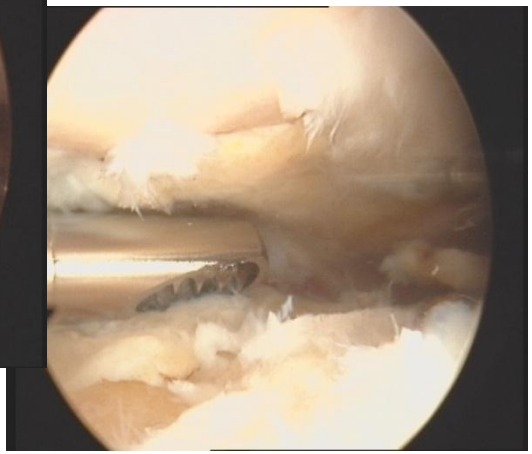
Comprehensive Care
History (late ‘90s): the core

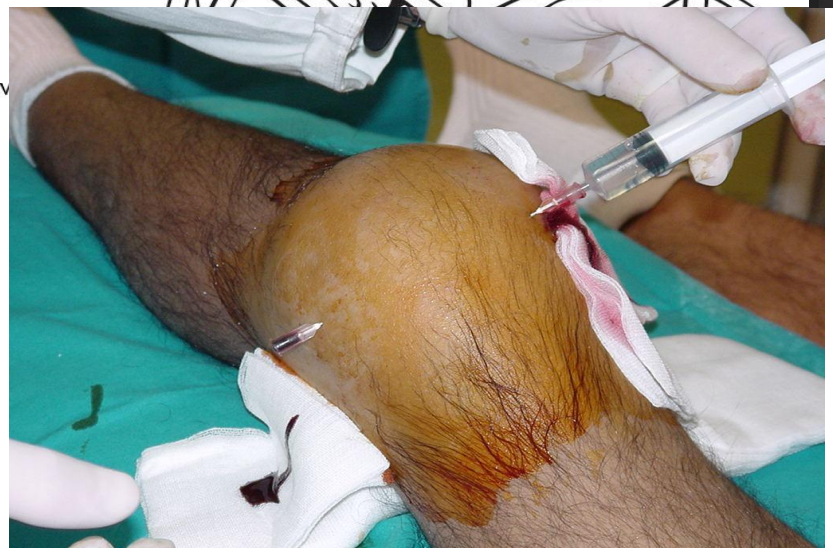


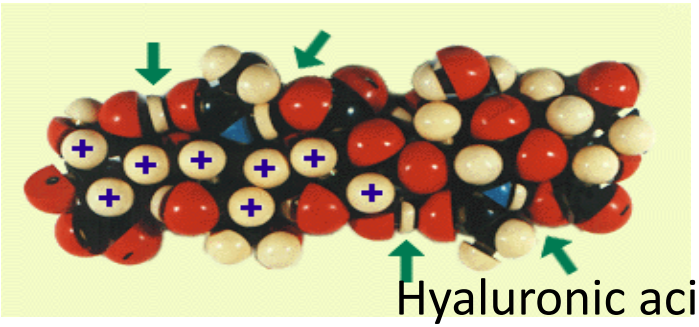
Orthopedic care

(Mini-invasive treatment)







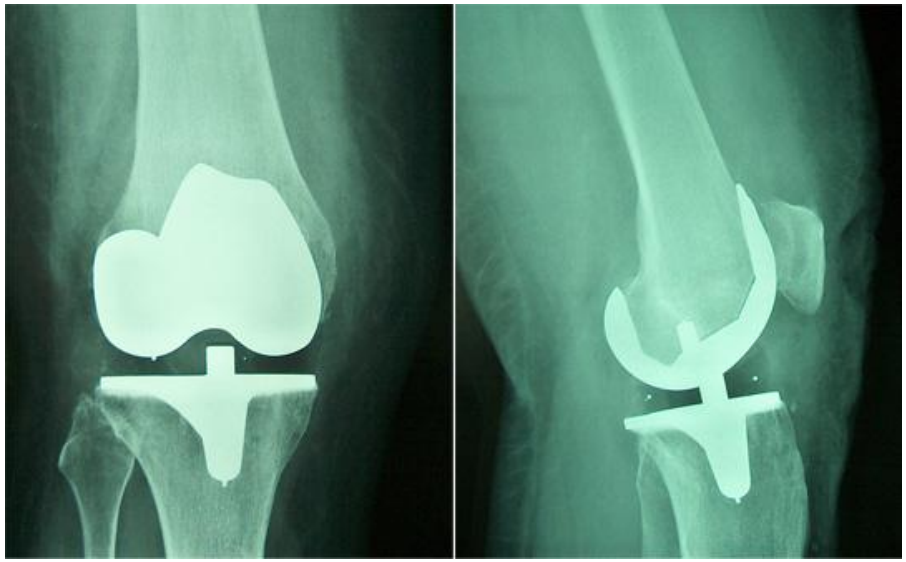


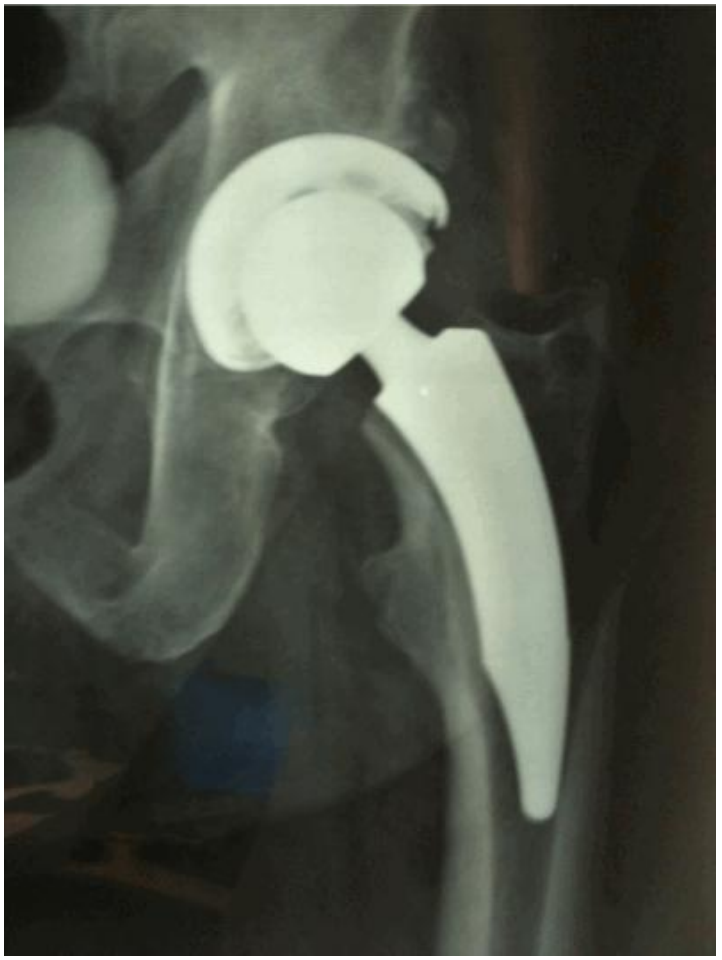
Hyaluronic acid

Comprehensive Care
1990 - 2000's

Orthopedic Surgery
in severe hemophilia patients…

THR, TKR
Ankle? Elbow?

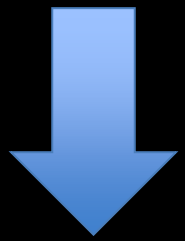




...even in patients with inhibitors

Comprehensive care

- Assessing multi-dimensional clinical outcomes and efficacy of treatment
- Preserving physical and psychological health in the long term

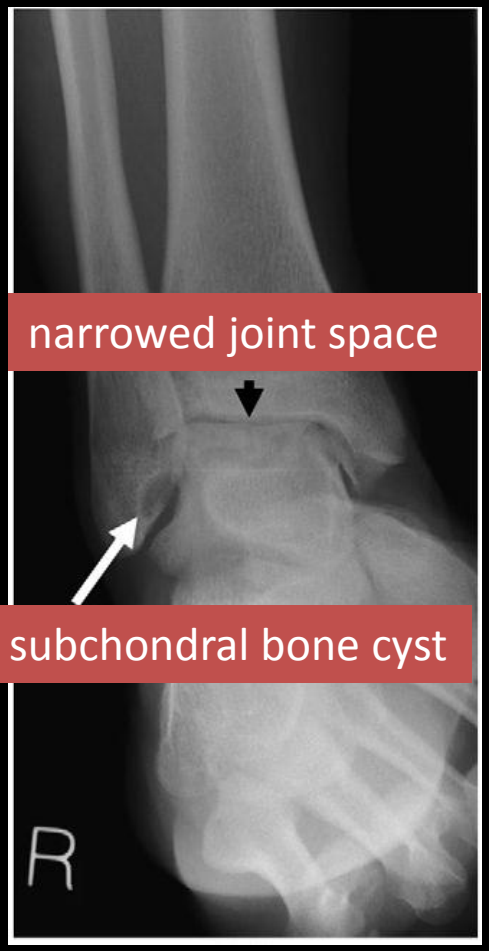


- Early (childhood) prevention of joint deterioration

- Preventing the negative impact of joint deterioration on clinical, social and quality of life variables

The traditional approach: X-ray

- Radiographic findings ➔ *radiodense effusion, osteonecrosis, osteoporosis, epiphyseal overgrowth, bone cysts, joint space irregularity and narrowing, bone fusion*



Bone changes: late finding

Early synovial changes: under-demonstrated

Early bone and cartilage damage: not appreciated

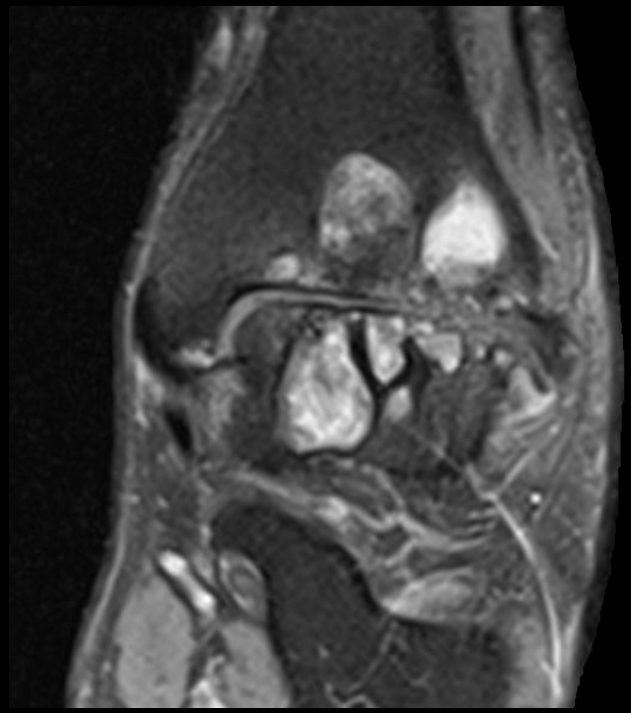
Cartilage destruction: not visualised "directly"

Low sensitivity for early changes of HA

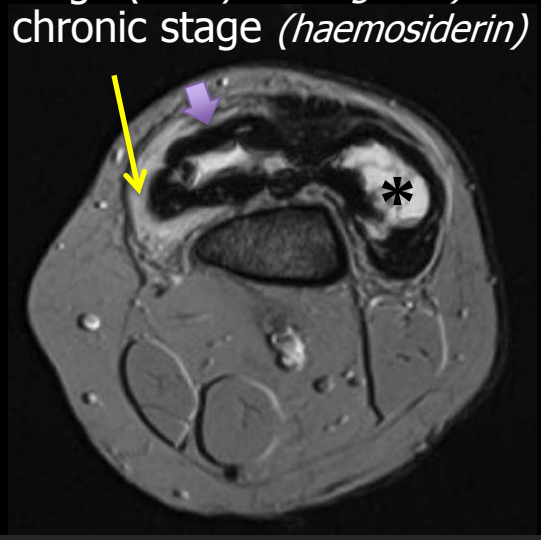
The new 'gold standard': MR imaging

- **Detailed information on all aspects of joints in haemophilia**
  - synovial thickening, bleeding, cartilage damage, early osteochondral abnormalities
- Chronic synovitis demonstrated in 50% of patients in which plain films were normal
- In patients with plain film abnormalities, MR imaging revealed more profound disease in 70%

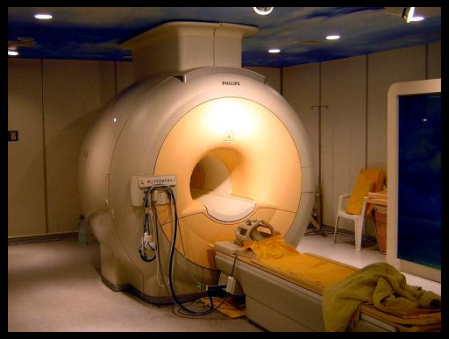
Rand et al. 1999
Pergantou et al. 2006



- GRE T2* MRI is able to detect blood products in the acute stage *(deoxyhaemoglobin)* and the chronic stage *(haemosiderin)*



MR imaging



→ **Gold Standard**

Limitations

- High-cost examination
- Difficult access → poor availability
- Poor repeatability
- Focused on one joint → selection bias
- Need for high magnetic field strengths and advanced sequences → cartilage imaging
- External reader → usually not dedicated
- Unnecessary anatomical details

Periodic MRI follow-up:
difficult to be performed!

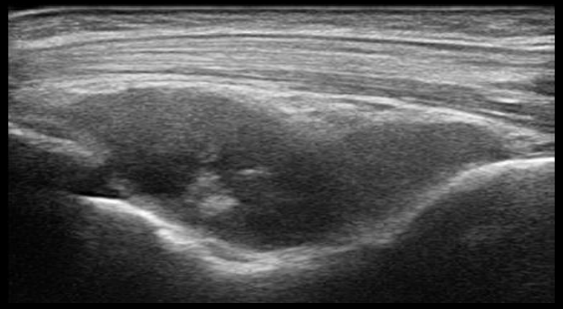
The role of ultrasonography in the diagnosis of the musculo-skeletal problems of haemophilia

F. QUEROL* and E. C. RODRIGUEZ-MERCHAN†

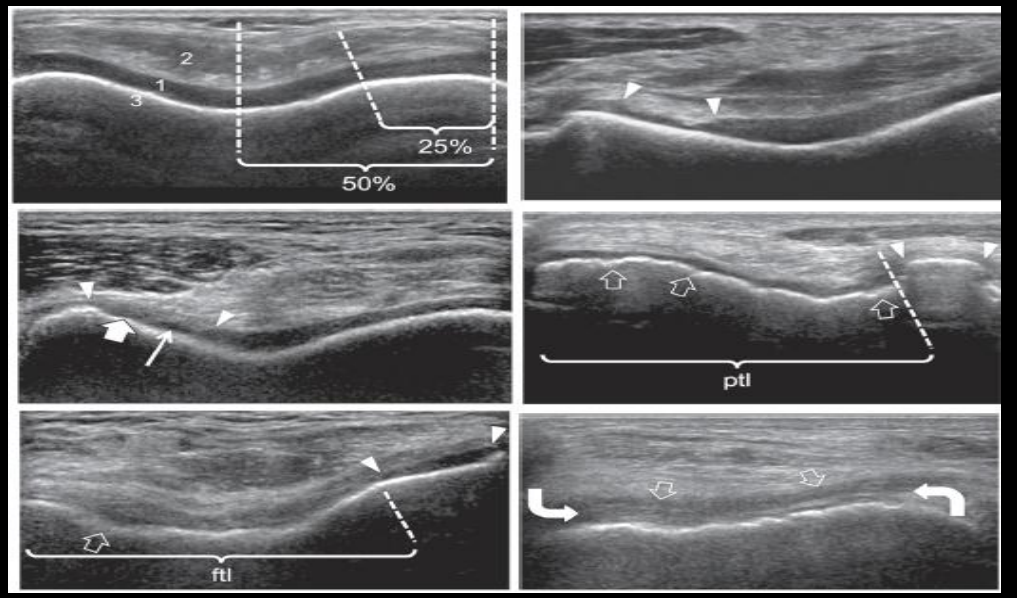
Haemophilia. 2012;18:e215-26.

1992	Daly BD [17]	Diagnosis of psoas haematoma
1992	Merchan ECR *et al.* [19]	Diagnosis of arthritic disease
1995	Rodriguez-Merchan EC [20]	Description of pseudotumour
2005	Balkan C *et al.* [21]	Diagnosis of psoas haematoma
2007	Goddard NJ *et al.* [22]	Diagnosis of synovitis
2008	Acharya SS *et al.* [23]	Comparative efficacy study of images
2008	Acharya SS [7]	Study of diagnostic approaches
2008	Antunes SV *et al.* [24]	Evaluate USG for diagnosis of arthritic disease
2010	Beyer R *et al.* [28]	Description of diagnostic tools for haematomas
2010	Beyer R *et al.* [29]	Description of diagnosis and treatment of haematomas
2010	Dimichele DM [30]	Role de USG Power-Doppler in haemophilic arthritic disease
2010	Khan U *et al.* [11]	Comparative study of imaging techniques
2011	Aznar *et al.* [31]	Describes results of USG monitoring haemarthrosis

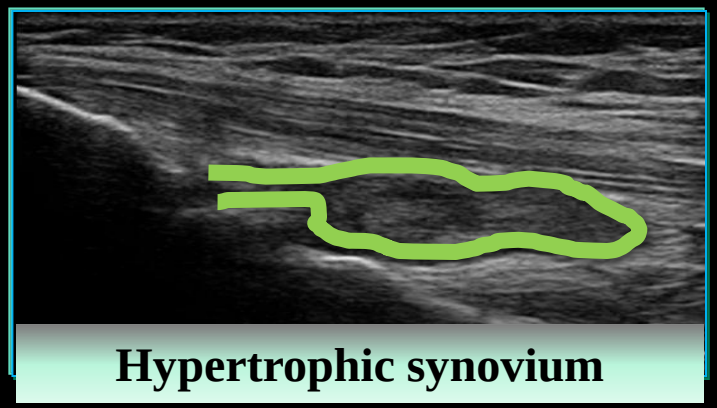
A newer approach: US



- An ideal means to assess the presence of:
  - Intra-articular effusion
  - Hypertrophic synovium
- Cartilage/bone damage
- Synovial hypertrophy
- the sequential stages of haematoma reabsorption



Examination time: 2 min/joint

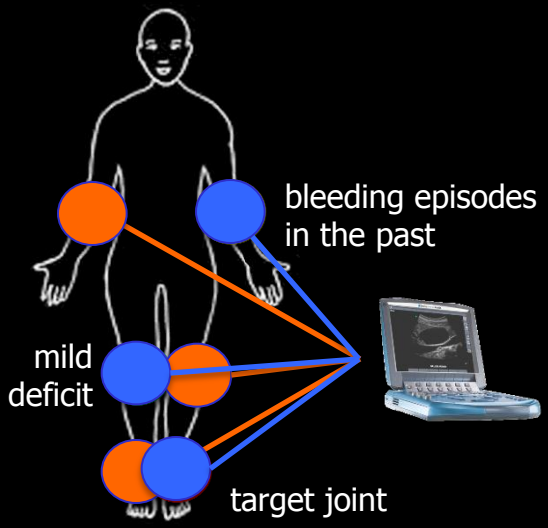


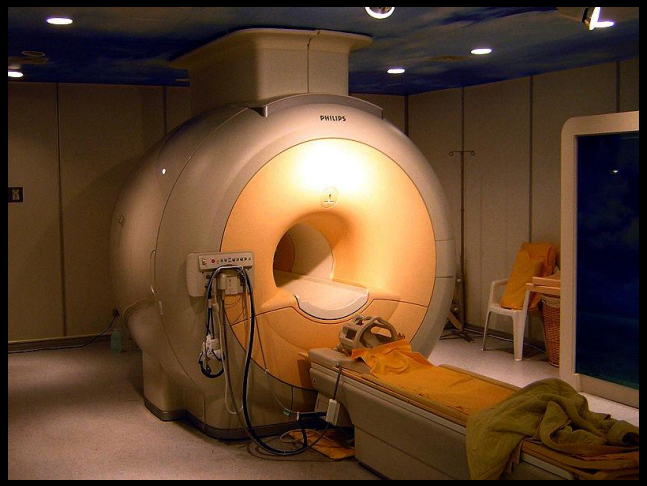
Development and Definition of a Simplified Scanning Procedure and Scoring Method for Haemophilia Early Arthropathy Detection with Ultrasound (HEAD-US)

Carlo Martinoli[1]; Ornella Della Casa Alberighi[3]; Giovanni Di Minno[5]; Ermelinda Graziano[6]; Angelo Claudio Molinari[4]; Gianluigi Pasta[7]; Giuseppe Russo[1]; Elena Santagostino[8]; Annarita Tagliaferri[9]; Alberto Tagliafico[2]; and Massimo Morfini[10]

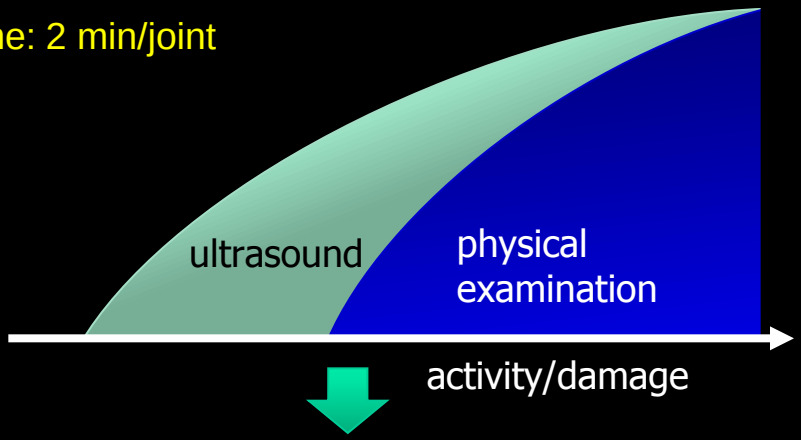
HEAD US

Haemophilia Early Arthropathy Detection with UltraSound





Examination time: 2 min/joint

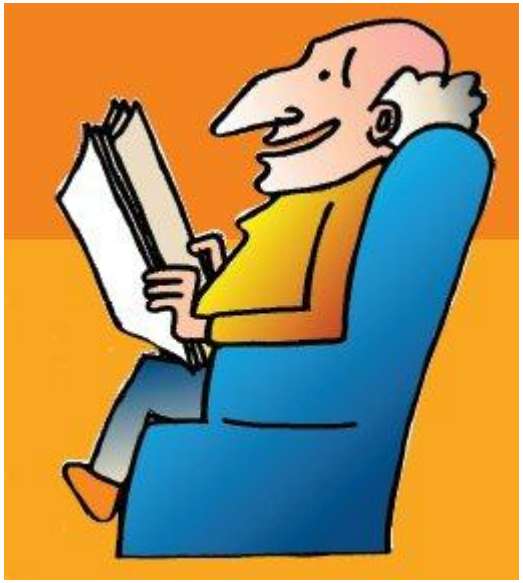


Unexpected results in asymptomatic joints

The evolving scenario of improved comprehensive care and prolonged life expectancy

- Cardiovascular disease
- Cancer
- Prostate diseases
- Renal disease
- Metabolic syndrome (obesity, diabetes, hypertension)
- Depression
- Erectile dysfunction
- Cataract, macular degeneration

Need for new specialty co-operation



BACKGROUND

IL TRATTAMENTO DEL BAMBINO AFFETTO DA EMOFILIA NON E' SOLO INFONDERE UN CERTO PRODOTTO IN UN CERTO MODO PER EVITARE LE CONSEGUENZE DELLE EMORRAGIE

LA *GLOBAL CARE DEL BAMBINO EMOFILICO* PREVEDE L'APPLICAZIONE DI TUTTE LE STRATEGIE CHE GARANTISCONO BUONA SALUTE FISICA E MENTALE AL PAZIENTE E ALLA FAMIGLIA*

Early (childhood) prevention of joint deterioration

**** SALUTE: Uno stato di completo benessere fisico, mentale e sociale e non semplicemente l' assenza di malattie o infermità.*** *(OMS)*

La profilassi, il regime di trattamento di scelta nel bambino

Joint Outcome Study

RISULTATI	Profilassi	on demand
n	32	33
Durata dello studio in giorni, media (totale)	1497 (47.895)	1490 (49.179)
Evidenza di danno alle articol., n (%)		
RM (n=27 profilassi; n=29 on demand)	2 (7%)	13 (45%)
Raggi X (n=27 profilassi; n=29 on demand)	1 (4)	5 (19)
No. infusioni di FVIII , totale	20.896	6.176
Media ± DS	653 ± 246	187 ± 100
U.I. di FVIII somministrato, totale	11'289'372	3'736'807
Media ± DS	352.793 ± 150.454	113.237 ± 65.494
Emorragie per paz. per anno		
Articolazioni, media ± DS (mediana)	0,63 ± 1,35 (0,20)	4,89 ± 3,57 (4,35)
Total, mean ± SD (median)	3,27 ± 6,24 (1,15)	17,69 ± 9,25 (17,13)

ACCESSO VENOSO

CATETERI VENOSI CENTRALI

I CVC sono in uso per favorire l'accesso venoso nei pazienti emofilici da 25 anni

Joshi R, 1982, Clin. Lab Haematol. 4(3), 319.

Oggi sono posizionati in circa il 30% dei pazienti con Emofilia grave

Geraghty S, 2006, Haemophilia 12(1), 75

Vantaggi:	Tutti paz:	accessibilità al sistema venoso infusione domiciliare
	On demand:	tempestività del trattamento
	Profilassi:	compliance alla prescrizione
	ITI:	applicabilità del programma
Svantaggi:	Tutti paz	Complicanze settiche e trombotiche

FOLLOW UP
nel bambino emofilico

CHEK UP periodico (mensile-trimestrale)

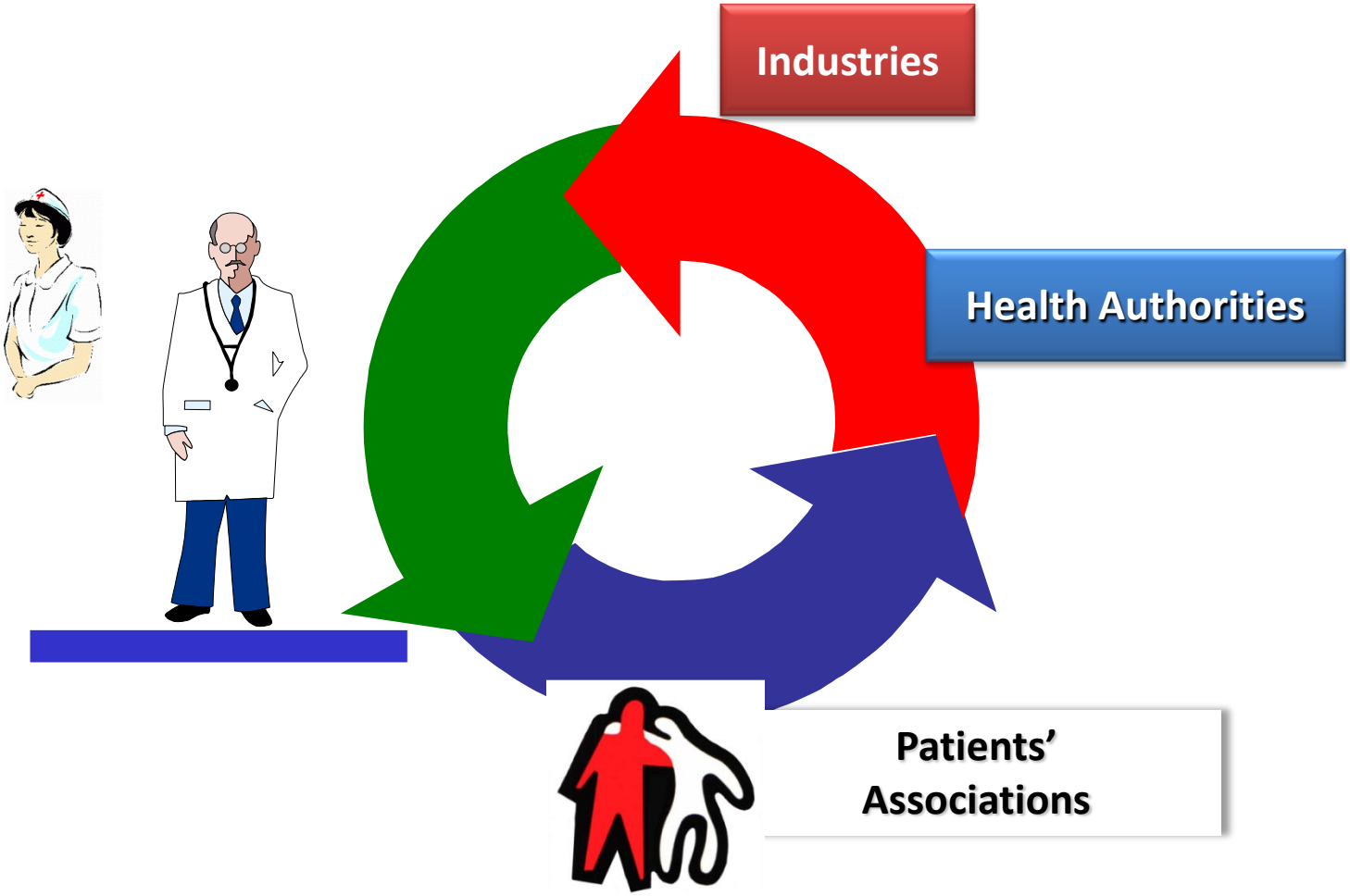
- ✓ Esame obiettivo con score ortopedico
- ✓ Valutazione accrescimento, adeguamento dose
- ✓ Verifica della **compliance al trattamento** (registro infusioni)
- ✓ Educazione/verifica capacità dei genitori all'infusione domiciliare
- ✓ Controllo del CVC venoso (previetà, emergenza)
- ✓ Controllo funzionalità fistola e monitoraggio complicanze cardiovascolari
- ✓ Work up di laboratorio (emocromo, ferritina, ricerca inibitore, dosaggio fattore pre e post infusione, sierologia infezioni trasfusionali)
- ✓ ***Aspetti sociali (qualità di vita del gruppo familiare, attività ludiche e sportive, frequenza scolastica)***

CLASSIFICAZONE DEGLI SPORT PER LIVELLO DI RISCHIO

Very Low	**Medium**	**High**
Swimming	Baseball	Alpine skiing(downhill)
Low	Road hockey	Football(tackle)
Bicycling	Soccer	Horseback riding
Golf	Squash / Raquetball	Ice hockey
Skating	Weight lifting	Rollerskating/ Rollerblading
Tennis	Windsurfing	Rugby
Low/ Medium	**Medium/ High**	Skateboarding
Basketball	Karate/ Judo	Waterskiing
Running		
Volleyball		
Nordic skiing(cross-country)		

modificato da http://www.hemophilia.ca/en/2.1.10.php

An essential cooperation



Conclusions

While awaiting for gene therapy in hemophilia….

Comprehensive care is aimed to warrant the best treatment and outcomes for hemophilia patients, i.e. the best quality of life.

An evolving, continuously improving task…

GRAZIE DELL’ATTENZIONE!

DIAGNOSI

Sempre più soggetti 'de novo'
Diagnosi ritardata , basata su eventi emorragici

Età alla diagnosi di 599 soggetti, nati 1980-1994

	Mediana (mesi)
gravi	5,8
moderati	9
Lievi	28,6
fratelli affetti	0,4
de novo	10,1

Chambost H, 2002, J. Pediatr. 141(4), 548.

PROBLEMATICHE SPECIFICHE DELL'EPOCA NEONATALE

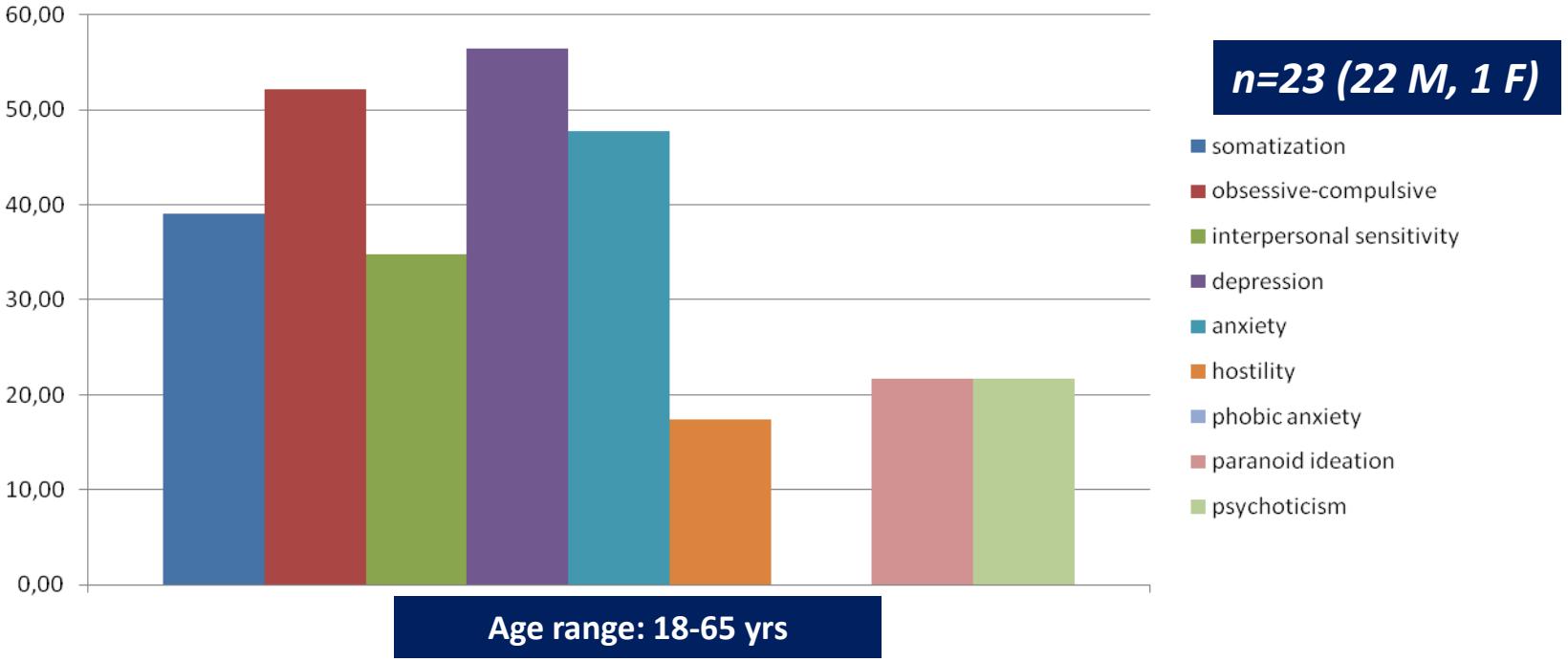
- ✓ In epoca neonatale l'emofilia è meno diagnosticata nonostante la sintomatologia emorragica
- ✓ Poco più del 50% degli emofilici gravi vengono diagnosticati alla nascita
- ✓ In famiglie note la diagnosi è posta al primo evento emorragico in non più del 60 % dei neonati e la diagnosi è ritardata nonostante emorragie inusuali fino all'87%
- ✓ <u>L'emorragia cerebrale può essere il primo sintomo</u>

Chambost H, 2002, J. Pediatr. 141(4), 548
Conway JH, 1994, Arch. Pediatr. Adolesc. Med 148(6), 589.
Ljung R, 1990, Acta Paediatr. Scand. 79(2), 196
Yoffe G, 1988, J. Pediatr. 113(2), 333

Psychological Support Program

Preliminary findings

SCL-90 – R (Symptom Check List-revised)



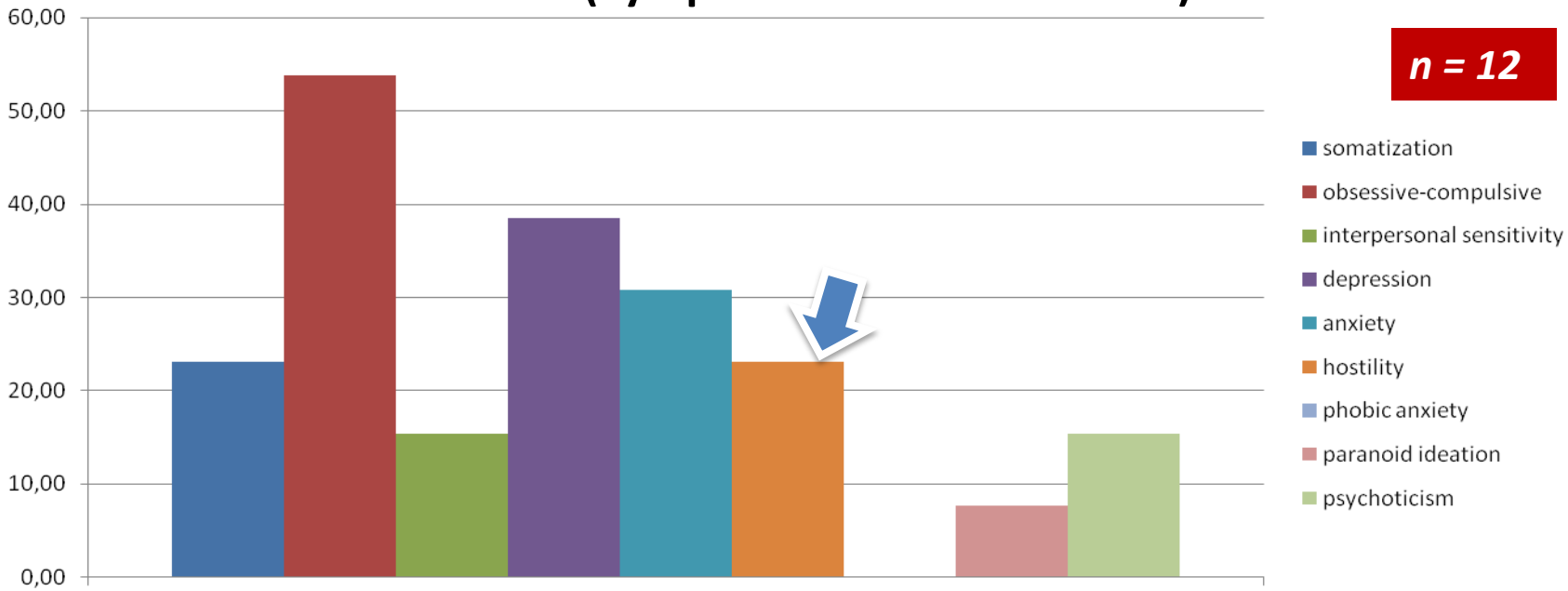
Age range: 18-65 yrs

Symptom	Prevalence
Somatization	9 (39.1%)
Obsessive-Compulsive	12 (52.2%)
Interpersonal Sensitivity	8 (34.8%)
Depression	13 (56.5%)
Anxiety	11 (47.8%)
Hostility	4 (17.4%)
Phobic Anxiety	0 (0%)
Paranoid Ideation	5 (21.8%)
Psychoticism	5 (21.8%)

Psychological Support Program

Preliminary findings

SCL-90 – R (Symptom Check List-revised)



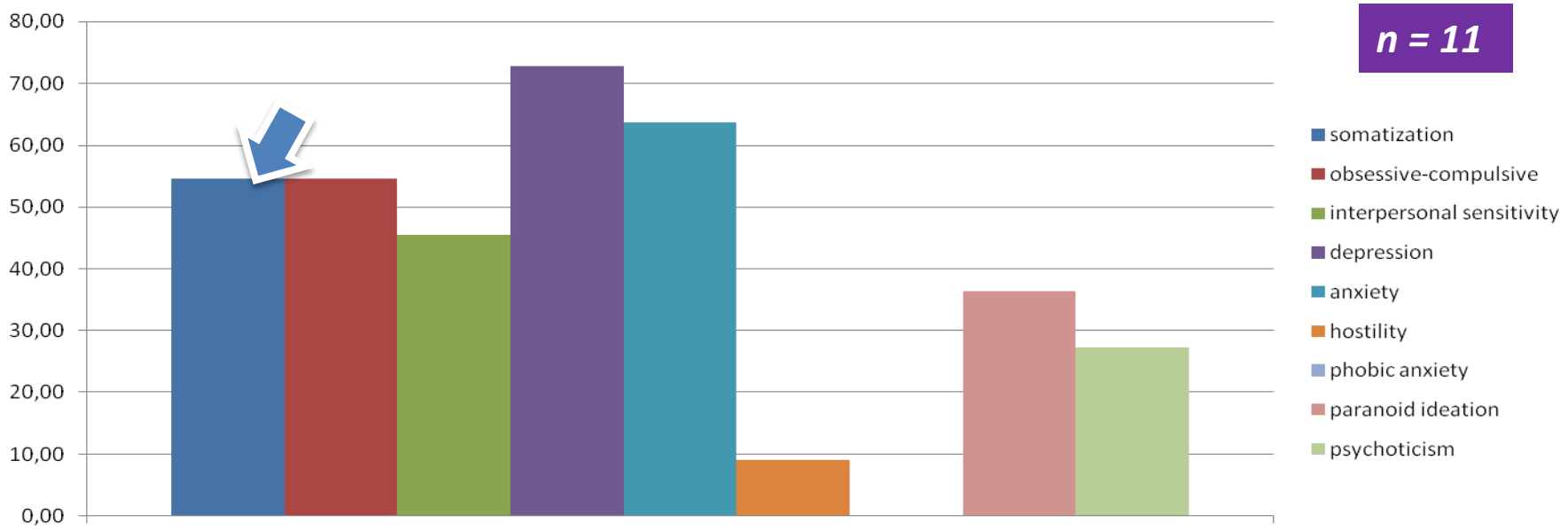
Age range: 18-40 yrs

Symptom	Prevalence
Somatization	3 (23.1%)
Obsessive-Compulsive	7 (53.9%)
Interpersonal Sensitivity	2 (15.4%)
Depression	5 (38.5%)
Anxiety	4 (30.1%)
Hostility	3 (23.1%)
Phobic Anxiety	0 (0%)
Paranoid Ideation	1 (7.7%)
Psychoticism	2 (15.4%)

Psychological Support Program

Preliminary findings

SCL-90 – R (Symptom Check List-revised)



Age range: 41-65 yrs

Symptom	Prevalence
Somatization	6 (54.6%)
Obsessive-Compulsive	6 (54.6%)
Interpersonal Sensitivity	5 (45.5%)
Depression	8 (72.7%)
Anxiety	7 (63.6%)
Hostility	1 (9.1%)
Phobic Anxiety	0 (0%)
Paranoid Ideation	4 (36.4%)
Psychoticism	3 (27.3%)

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.

***Obiettivo*: Confrontare l'efficacia della profilassi con infusione di FVIII, somministrato a giorni alterni, rispetto alla terapia on demand con dosi massicce, nella prevenzione dei danni alle articolazioni**

Psychological Support Program

Preliminary findings

ZUNG (Self Depression Scale, SDS)

Normal	Mildly Depressed	Moderatly depressed	Severely depressed
18	2	2	0

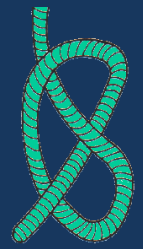
Haemo-A QoI

Low	Medium-low	Medium	Medium-good	Good	Very good
3	5	5	4	2	4*

**3 <22 yrs, on prophylaxis*

QoL tests

Very poor	Not very good	Good	Very good
1 (4/10)	3 (6-7/10)	7 (8/10)	12 (9-10/10)



LA GESTIONE *GLOBALE* DEL PAZIENTE EMOFILICO IN ETA' PEDIATRICA

Validations

US vs Clinical Examination (HJHS)

US vs X-ray (Pettersson score)

US vs MRI (Compatible scale)

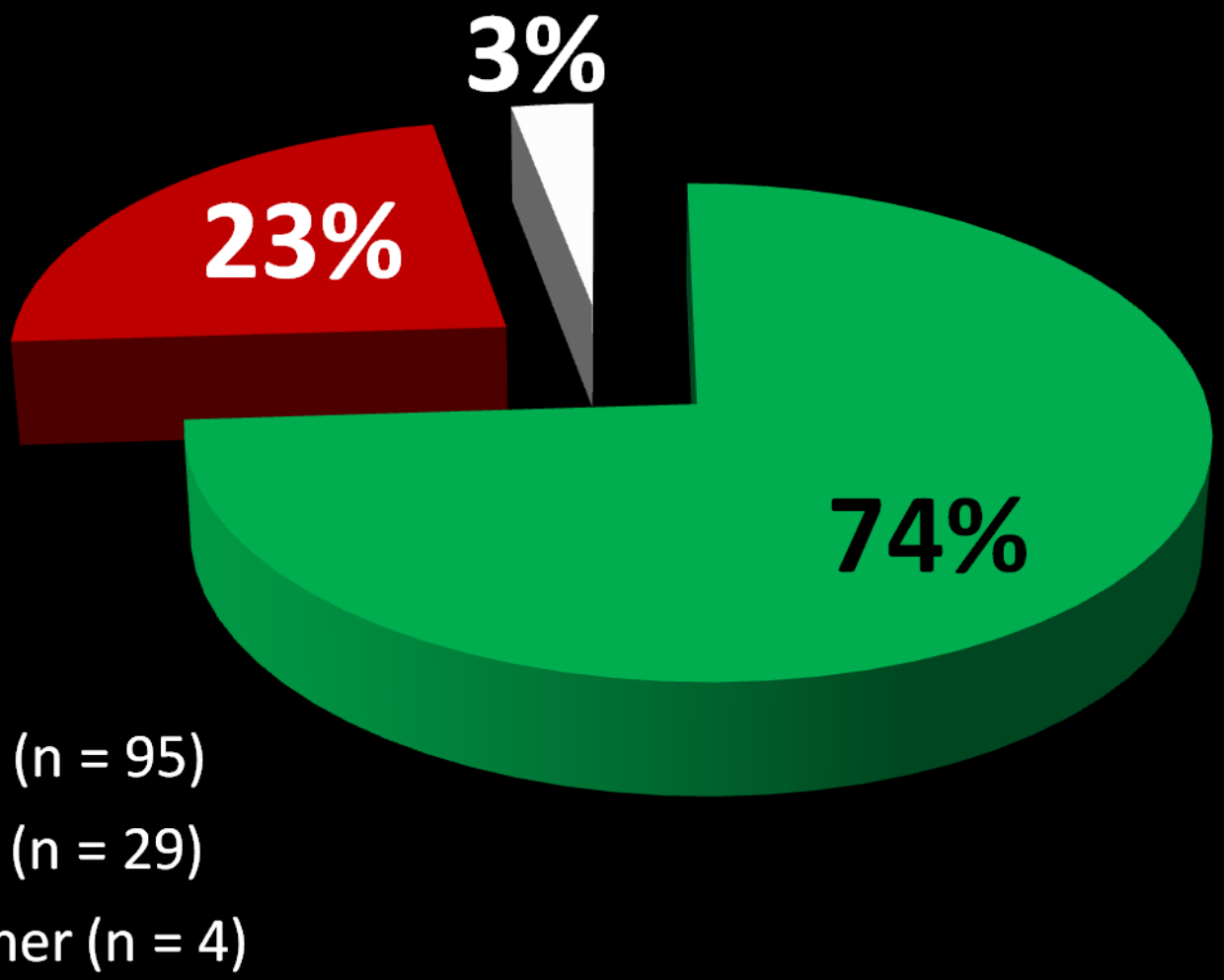
… Hemosiderin visualisation …

… Power Doppler positivity …

ITALIAN US TRAINING

128 patients with bleeding disorders

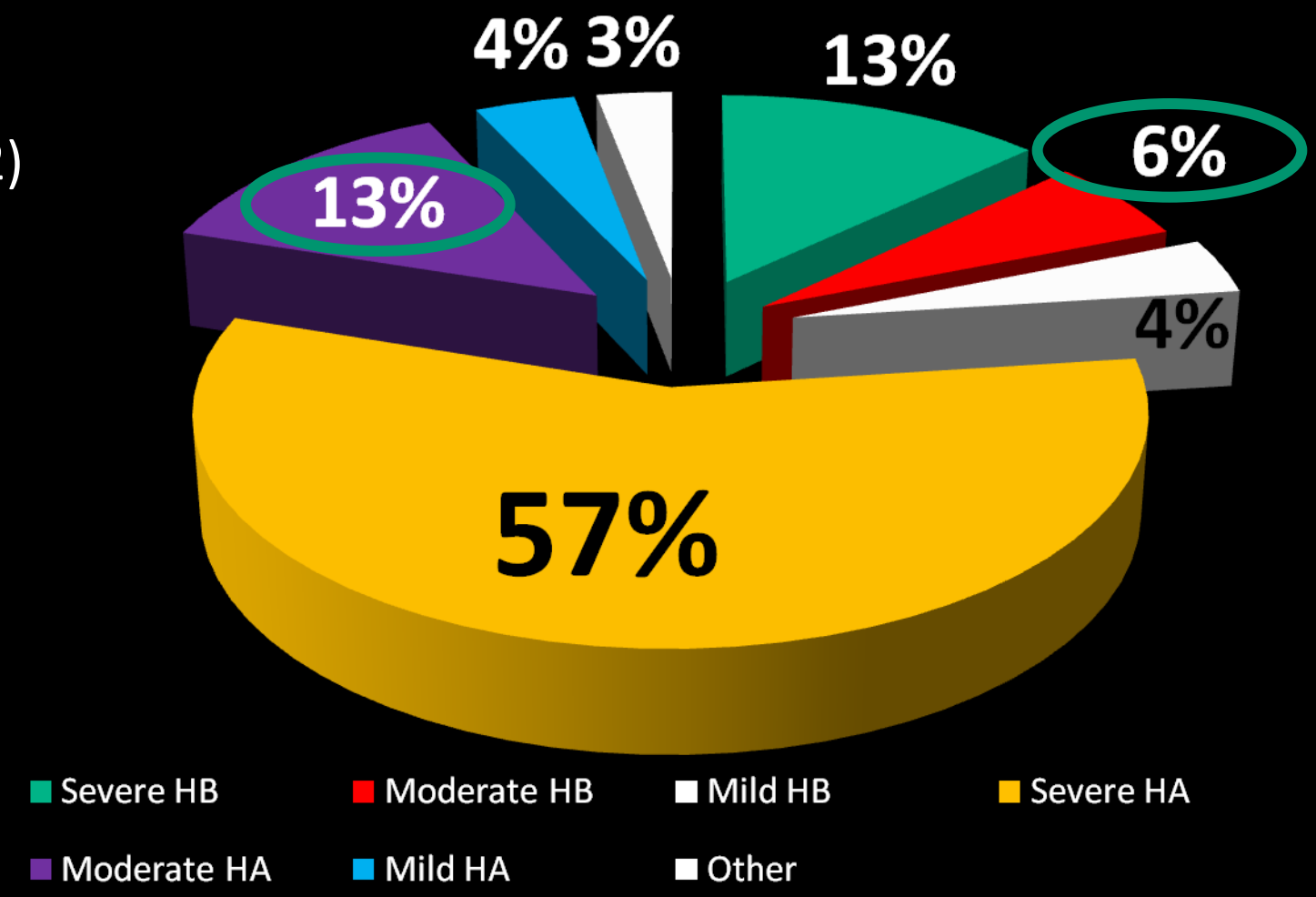
- PAVIA
- PALERMO (x2)
- VERONA
- BOLOGNA
- SASSARI
- ROMA
- BARI
- TORINO
- COSENZA



ITALIAN US TRAINING

124 haemophilia patients

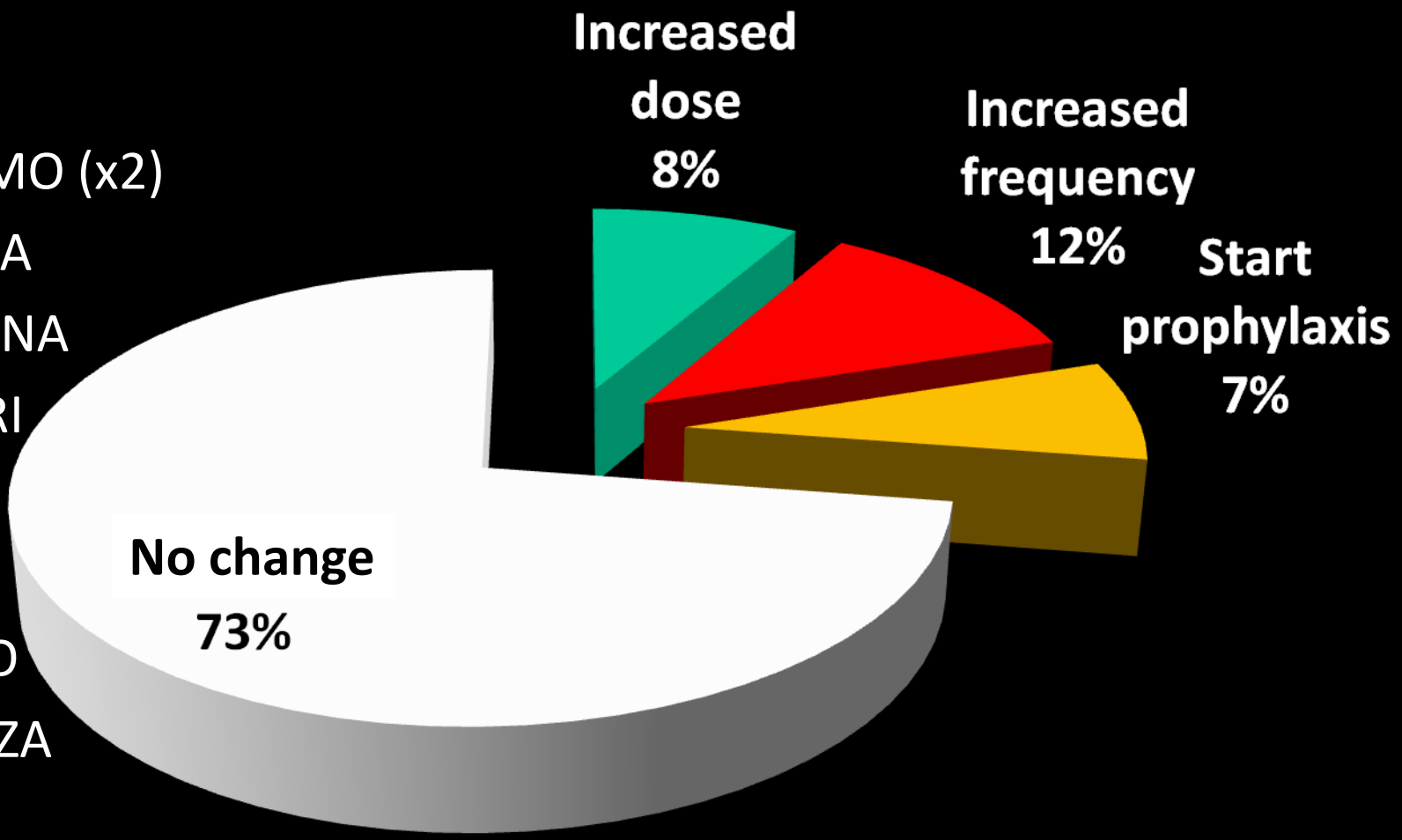
- PAVIA
- PALERMO (x2)
- VERONA
- BOLOGNA
- SASSARI
- ROMA
- BARI
- TORINO
- COSENZA



ITALIAN US TRAINING

95 haemophilia A patients

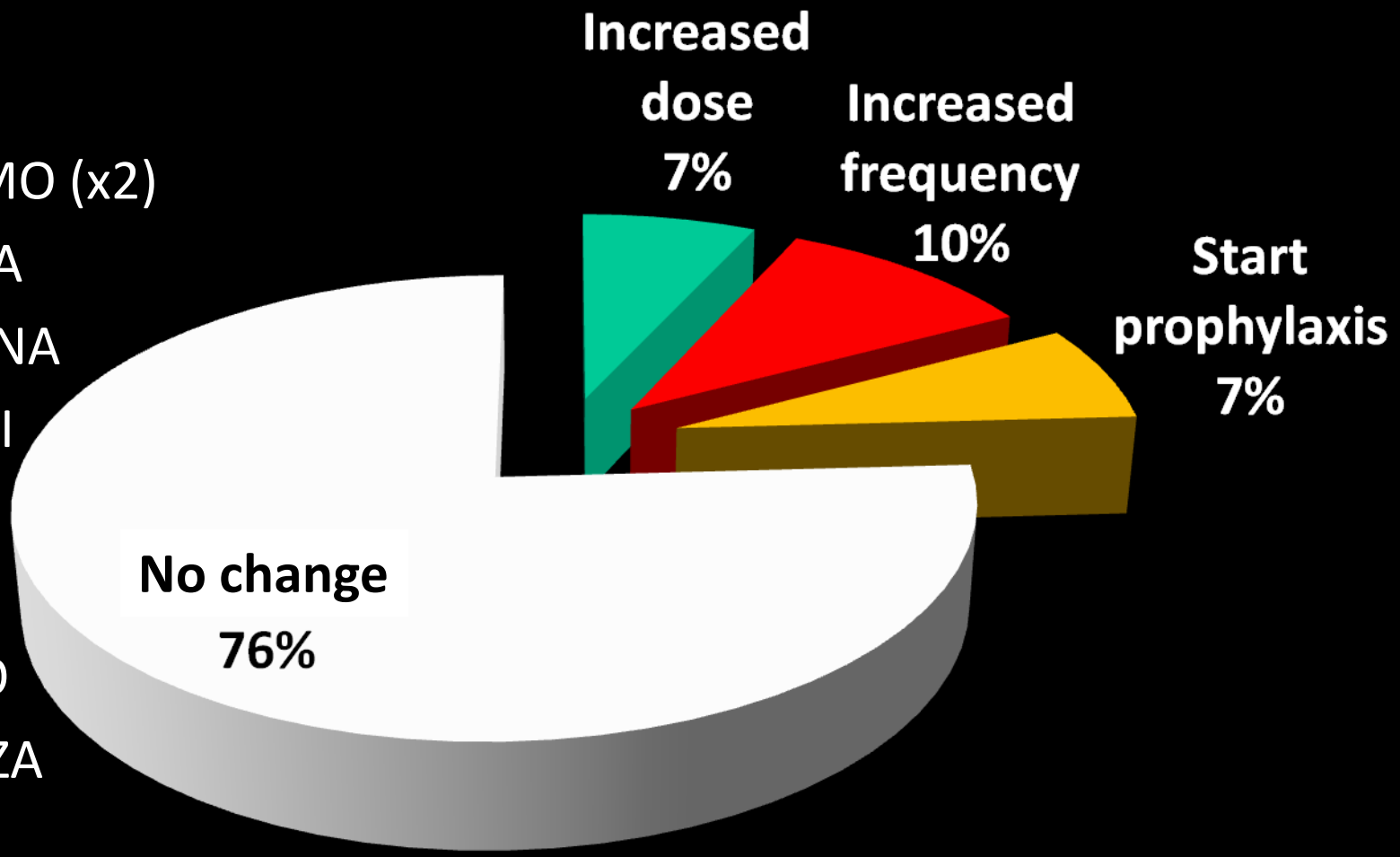
- PAVIA
- PALERMO (x2)
- VERONA
- BOLOGNA
- SASSARI
- ROMA
- BARI
- TORINO
- COSENZA



ITALIAN US TRAINING

29 haemophilia B patients

- PAVIA
- PALERMO (x2)
- VERONA
- BOLOGNA
- SASSARI
- ROMA
- BARI
- TORINO
- COSENZA



ITALIAN US TRAINING

Limitations

… Unexpected changes in about 25–30% of evaluated subjects …