7^ Conferenza Nazionale dei Servizi Trasfusionali
Vicenza | 24-26 maggio 2023
SIMTI

Diagnosi precoce di carcinoma della mammella in una paziente con Emofilia A Acquisita (EAA): un caso.

Anna Chiara Giuffrida

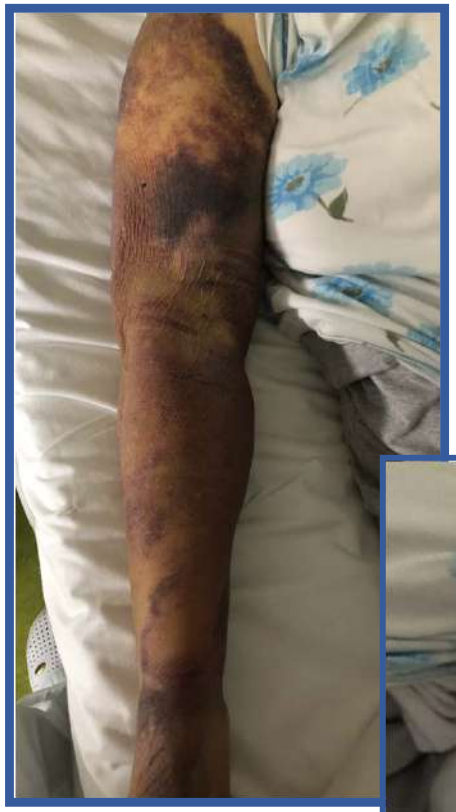
Centro Emofilia-UOC Medicina Trasfusionale

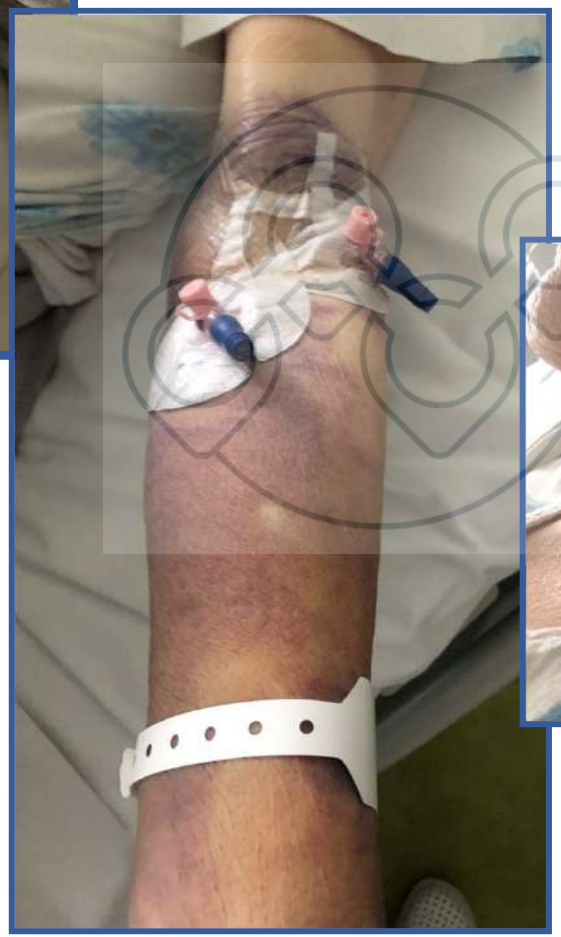
AOUI VERONA

La sottoscritta, in qualità di Presentatrice
dichiara che

nell’esercizio della Sua funzione e per l’evento in oggetto,
NON È IN ALCUN MODO
portatrice di interessi commerciali propri o di terzi; e che gli eventuali rapporti avuti negli ultimi due anni con soggetti portatori di interessi commerciali non sono tali da permettere a tali soggetti di influenzare le sue funzioni al fine di trarne vantaggio.

Anna Chiara Giuffrida





ACG1

Anna Chiara Giuffrida

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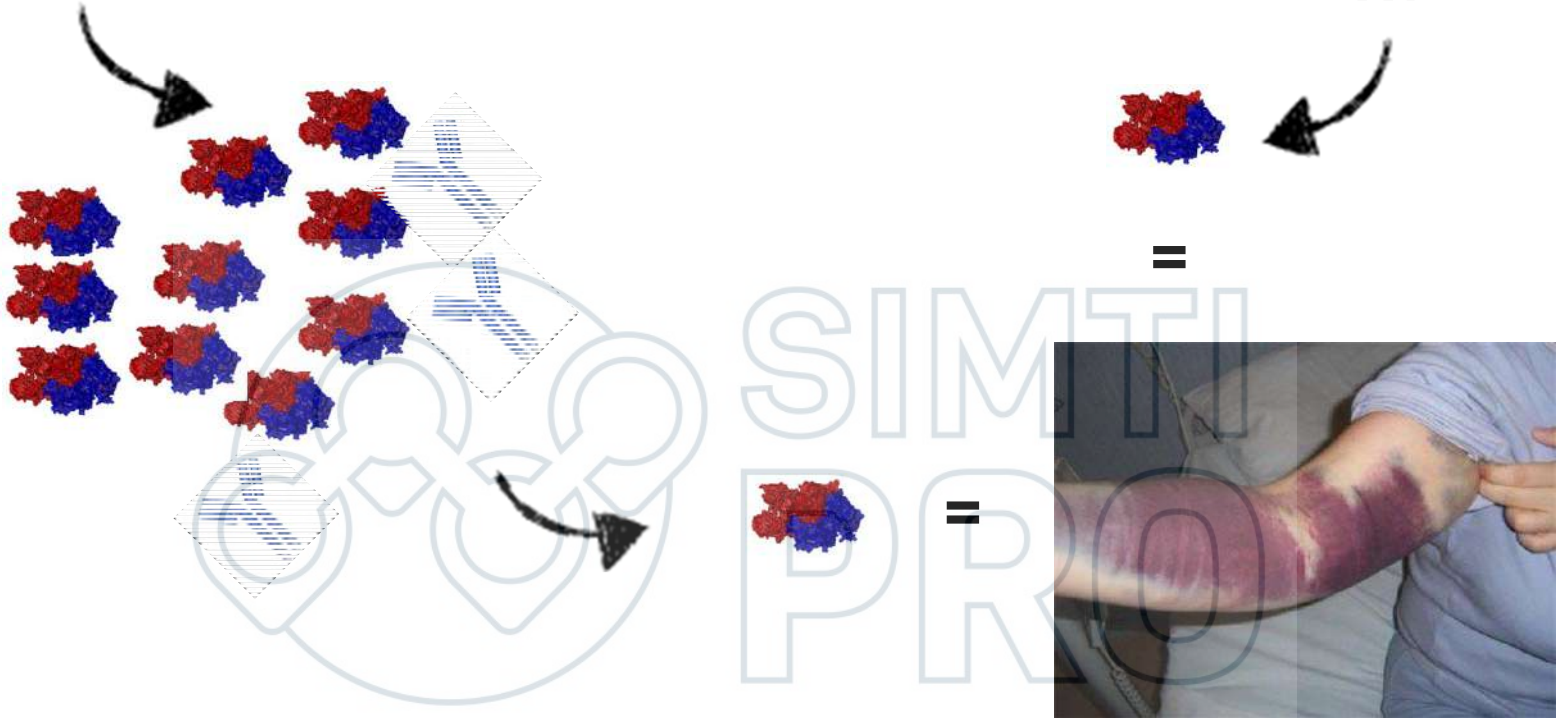
Diapositiva 3

ACG1 Vi presento l'emofilia acquisita..
Ematomi estesi spontanei, dopo posizionamento di accesso periferico
Da notare: le tre foto a destra sono della stessa paziente!
Anna Chiara Giuffrida; 21/05/2023

Emofilia Acquisita*



*Sindrome emorragica acquisita della coagulazione, caratterizzata dal deficit di FVIII secondario alla produzione di autoanticorpi che si legano al FVIII circolante, neutralizzandone l'attività e/o aumentando la clearance.
Colpisce uomini e donne.

Anna Chiara Giuffrida

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Journal of Thrombosis and Haemostasis, **10**: 622–631 DOI: 10.1111/j.1538-7836.2012.04654.x

ORIGINAL ARTICLE

Demographic and clinical data in acquired hemophilia A: results from the European Acquired Haemophilia Registry (EACH2)

P. KNOEBL,* P. MARCO,† F. BAUDO,‡ P. COLLINS,§ A. HUTH-KÜHNE,¶ L. NEMES,** F. PELLEGRINI,†† L. TENGBORN,‡‡ and H. LÉVESQUE,§§ ON BEHALF OF THE EACH2 REGISTRY CONTRIBUTORS[1]

**Division of Hematology and Hemostasis, Department of Medicine 1, Medical University of Vienna, Vienna, Austria; †Unidad de Hemostasia y Trombosis, Servicio de Hematología, Hospital General Universitario, Alicante, Spain; ‡Thrombosis Hemostasis Unit, Niguarda Hospital, Milan, Italy; §Arthur Bloom Haemophilia Centre, School of Medicine, University Hospital of Wales, Cardiff University, Cardiff, UK; ¶SRH Kurpfalzkrankenhaus Heidelberg GmbH and Hemophilia Center, Heidelberg, Germany; **National Hemophilia Center and Hemostasis Department, State Health Centre, Budapest, Hungary; ††Unit of Biostatistics, Department of Clinical Pharmacology and Epidemiology, Consorzio Mario Negri Sud, Santa Maria Imbaro, Chieti, Italy; ‡‡Clinical Coagulation Research Unit, Skåne University Hospital, Malmö, Sweden; and §§Department of Internal Medicine, Rouen University Hospital, Rouen Cedex, France*

To cite this article: Knoebl P, Marco P, Baudo F, Collins P, Huth-Kühne A, Nemes L, Pellegrini F, Tengborn L, Lévesque H, on behalf of the EACH2 Registry Contributors. Demographic and clinical data in acquired hemophilia A: results from the European Acquired Haemophilia Registry (EACH2). *J Thromb Haemost* 2012; **10**: 622–31.

Summary. *Background:* Acquired hemophilia A (AHA) is a rare autoimmune disease caused by autoantibodies against coagulation factor VIII and characterized by spontaneous hemorrhage in patients with no previous family or personal history of bleeding. Although data on several AHA cohorts have been collected, limited information is available on the optimal management of AHA. *Objectives:* The European Acquired Hemophilia Registry (EACH2) was established to

initiation in 33.5%. Four hundred and seventy-seven patients underwent immunosuppression, and 72.6% achieved complete remission. *Conclusions:* Representing the largest collection of consecutive AHA cases to date, EACH2 facilitates the analysis of a variety of open questions in AHA.

Keywords: acquired hemophilia, demographics, diagnosis, outcome, registry, treatment.

EACH Registry 501 pts →

idiopatica: 52%; secondaria a mal autoimmune (11,6%) e neoplasia (11,8%)

→ **nel 89% diagnosi per emorragia; in circa 9% per APTT allungato**

→ **emorragia spontanea (77,4%); post-trauma (8,4%); post-chir (8,2%)**
sito di emorragia: per lo più sottocute, muscolo e retroperitoneo;

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Table 4 Impact of diagnostic delay

Time bleeding to definite diagnosis	No. of patients (%)	Median FVIII activity [U dL^{-1} (IQR)]	Median inhibitor titer [BU mL^{-1} (IQR)]	Hb [g dL^{-1} (IQR)]	Severe bleeding [*n* (%)]	Median time to start of hemostatic therapy [days (IQR)]	Median time to bleeding resolved [days (IQR)]
0–1 day	174 (38.2)	2 (1–4)	14 (6–58)	9.4 (7.6–9.4)	121 (70.0)	1 (0–3)	4 (2–11)
2–7 days	121 (26.5)	2 (1–5)	15 (5–41)	8.5 (7.1–10.7)	95 (78.5)	4 (2–5)	4 (2–9)
> 7 days	161 (35.3)	2 (0–6)	7 (2–30)	8.9 (7–11.3)	108 (67.1)	20 (12–43)	5 (2–13)
*P**	NA	NS	NS	NS	NS	< 0.0001	NS

IQR, interquartile range; BU, Bethesda Units; Hb, hemoglobin; NA, not applicable; NS, not significant. Data are reported as *n* (%) and median (IQR) for categorical and continuous variables, respectively. *Kruskal–Wallis test.

Keywords: acquired hemophilia, demographics, diagnosis, outcome, registry, treatment.

EACH Registry 501 pts

→ **idiopatica: 52%; secondaria a mal autoimmune (11,6%) e neoplasia (11,8%)**

→ **nel 89% diagnosi per emorragia; in circa 9% per APTT allungato**

→ **emorragia spontanea (77,4%); post-trauma (8,4%); post-chir (8,2%)**
sito di emorragia: per lo più sottocute, muscolo e retroperitoneo;

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Diagnosi

Emocromo
APTT, PT, fibrinogeno
Test di miscela (anche dopo 2 ore!)

Dosaggio del FVIII
Ricerca di inibitore contro il FVIII
Titolazione dell'inibitore

Terapia

ANTIEMORRAGICA

IMMUNOSOPPRESSIVA

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Case Report

Una donna di 74 anni è stata ricoverata nel 2022 per diatesi emorragica (ematomi diffusi agli arti inferiori, all'arto superiore destro e alla parete addominale), anemia e alterazione della coagulazione (APTT: 2,84 ratio; test di miscela: mancata correzione di APTT anche dopo 2 ore di incubazione; dosaggio del Fattore VIII: 3,6%; titolo dell'inibitore: 113 UB). All'anamnesi da segnalare: ipertensione arteriosa, tiroidite cronica autoimmune, pregresso meningioma. E' stato iniziata terapia antiemorragica con Fattore VII attivato ricombinante (rFVIIa) alla dose di 90 microg/kg e.v. inizialmente ogni 6 ore, poi a scalare sulla base della clinica (miglioramento degli ematomi, assenza di nuovi eventi emorragici, normalizzazione del dato di emoglobina). Si è inoltre iniziata terapia steroidea (prednisone 1 mg/Kg/die per os) e successivamente ciclofosfamide (1 mg/Kg/die per os per quattro settimane): nel corso delle settimane si è assistito a riduzione progressiva dell'APTT, incremento del FVIII fino a normalizzazione, contestuale riduzione e scomparsa dell'inibitore.

Nella nostra Azienda è abitudine lo studio dei pazienti affetti da AHA per l'eventuale diagnosi di neoplasie medianti test di laboratorio (marcatori tumorali) e indagini radiologiche (rx-torace, ecografia addome completo, TC e PET-scan). Nel nostro caso, in quadro asintomatico, si è evidenziato alla mammografia nodulo della mammella destra (TC stagnazione e TC PET negativi per secondarismi). L'agobiopsia, eseguita in regime di ricovero e previa terapia antiemorragica, ha concluso carcinoma globulare infiltrante. La paziente è stata successivamente sottoposta a tumorectomia e radioterapia adiuvante. La paziente è in remissione e sta proseguendo ormonoterapia adiuvante; i controlli di laboratorio hanno mostrato normalizzazione del FVIII ed assenza di inibitore.

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Acquired haemophilia A: Italian Consensus Recommendations on diagnosis, general management and treatment of bleeding

Table V - *Summary of recommendations for the diagnosis, general management and treatment of bleeding and monitoring of patients with acquired haemophilia A*

RECOMMENDATION	STRENGTH^
A. DIAGNOSIS	
The diagnosis of AHA should be considered in the event of a sudden onset of bleeding in a patient without a personal and family history of bleeding, who exhibits an isolated prolonged aPTT, not corrected in a mixing test, immediately and after incubation for 2 hours at 37 °C	**1B**
The mixing test should be available also in non-specialised laboratories under ordinary and urgent circumstances	
The laboratory diagnosis of AHA should be made/confirmed by specialised laboratories that work in close collaboration with centres specialised in the diagnosis and treatment of patients with haemophilia and other coagulopathies	
B. GENERAL ASPECTS OF MANAGEMENT	
Patients with AHA should preferentially be managed in specialised centres, to which they should be immediately referred at the time of the clinical suspicion of the disease. If this referral is not readily feasible, bleeding episodes should be treated locally in close collaboration with a specialised centre or based on already shared protocols, to ensure prompt implementation of the most appropriate treatment of bleeding, as well as the best global management, in the context of a multidisciplinary approach	
Invasive procedures should be avoided, when possible, in patients with suspected AHA until the diagnosis has been made	**1C**
The recognition of associated conditions triggering the inhibitor development (e.g., malignancies, drugs) is crucial from a prognostic point of view, since treatment of such condition can lead to disappearance/significant reduction of the inhibitor	**1C**
The diagnosis of AHA should be followed by prompt initiation of immunosuppressive therapy to eradicate the inhibitor	**1B**
In the absence of bleeding, paediatric or post-partum cases or those clearly secondary to use of drugs can be exceptions to the immediate initiation of eradication treatment, as spontaneous resolution of the autoimmune phenomenon may occur	**2B**
If a "wait and watch" approach is adopted, immunosuppressive therapy aimed at inhibitor eradication can nevertheless be started if a rapid reduction of the inhibitor titre is not observed or bleeding symptoms occur	**2B**

A. Coppola et Al. 2022 Blood Transf. 20:245-262

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Core tip: Acquired hemophilia A (AHA) is a rare hemorrhagic disease usually affecting the elderly, involving reduced coagulation factor Ⅷ activity. Malignancies are reported to occur in association with 10%-15% of patients with AHA. We report two cases of AHA in solid cancer, namely, gastric cancer and hepatocellular carcinoma. Hemostasis was fully achieved owing to eradication of inhibitor against factor Ⅷ, however, both patients died within 1 year due to cancer progression. Successful treatment for AHA in solid cancer can be difficult because not only active hemorrhage management and inhibitor eradication but also treatment of the underlying malignancy is required.

Saito et Al. 2018 World J Clin Cases. 8(14):781-785

In AHA secondary to neoplasia, there is no predominant oncological entity, although it seems more frequent among solid organ neoplasms.[23] Sometimes it precedes tumor diagnosis in months, so it can be labeled in this context as a paraneoplastic syndrome.[23–32] Sometimes, the detection of an inhibitor takes place after the start of treatment of the specific neoplasm, and it is very difficult to exclude the influence of other factors such as immunosuppressive treatment, chemotherapy and radiotherapy used in its genesis. Another hypothesis to take into account is the non-causal association between neoplasms and AHA, since both are pathologies of advanced age that could coexist.[23,29]

M.E. Mingot-Castellano et Al. 2022 J Blood Med. 13:691-710

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Accepted: 1 September 2017
DOI: 10.1111/hae.13355

REVIEW ARTICLE

WILEY Haemophilia

Acquired haemophilia in cancer: A systematic and critical literature review

M. Napolitano[1] | S. Siragusa[1] | S. Mancuso[1] | C. M. Kessler[2]

Limite temporale: 1965-2016
Criteri di inclusione: neoplasia (solida e/o ematologica) prima o entro i 6 mesi dalla diagnosi di AHA.
105 pts inclusi nella review (F: 40; M: 65; Età media in entrambi sessi: 68 aa)
60 pts con tumori solidi (k prostata: 25,3%, k polmone: 15,8%, k colon: 9,5%) e 45 pts con malattie ematologiche (linfoma: 24,4%, LLC: 22,3%, MMC: 13,3%, LMA: 9%, MDS: 8,8%).
Sanguinamenti: mucosi e cutanei

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Accepted: 1 September 2017
DOI: 10.1111/hae.13355

REVIEW ARTICLE

WILEY Haemophilia

Acquired haemophilia in cancer: A systematic and critical literature review

M. Napolitano[1] | S. Siragusa[1] | S. Mancuso[1] | C. M. Kessler[2]

Conclusion: CR was best achieved when successful and complete elimination of autoantibodies occurred contemporaneously with the successful treatment of the underlying malignancy. In some cases, recurrent autoantibodies were harbingers of relapsed cancer. Type of cancer, inhibitor titer, treatments administered for bleeding control and inhibitor eradication did not significantly affect clinical outcome of analyzed cases.

Limite te
Criteri di
105 pts
60 pts
ematolo
Sanguinamenti: mucosi e cutanei

6 mesi dalla diagnosi di AHA.
68 aa)
olon: 9,5%) e 45 pts con malattie
DS: 8,8%).

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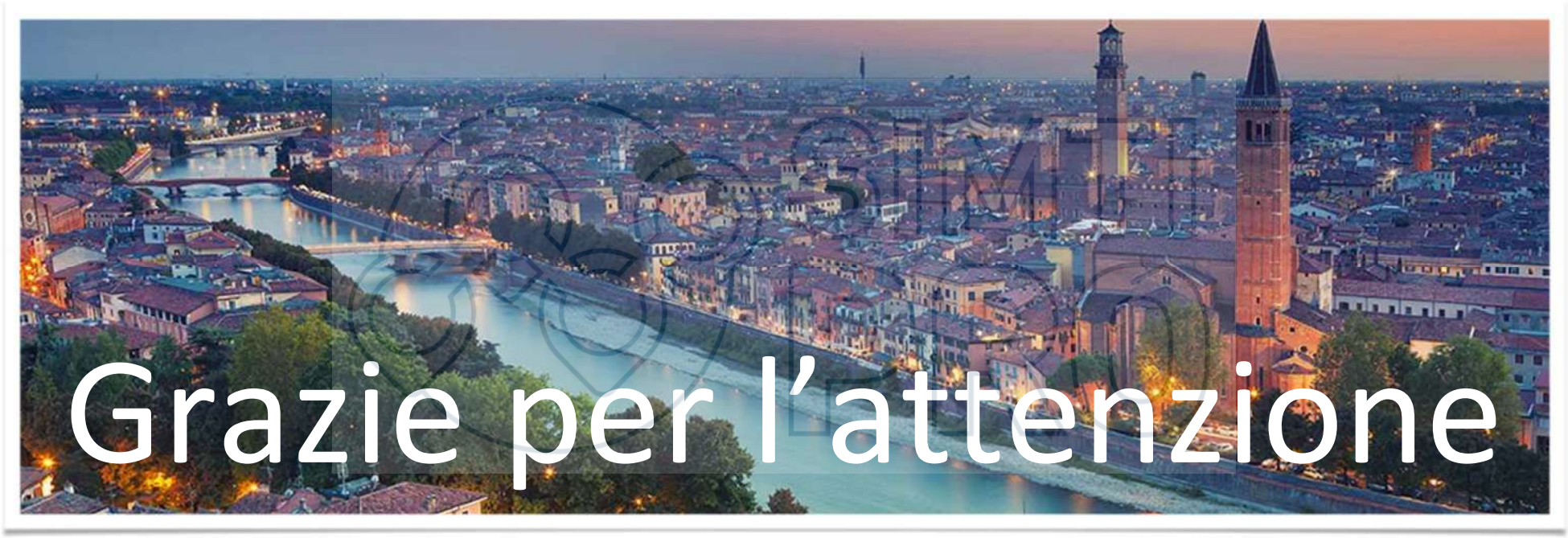
Anamnesi familiare: negativa per MEC
Anamnesi Patologica Remota: considerare abitudini ed attività; interventi chirurgici e patologie concomitanti.
Anamnesi emorragica: silente fino al momento "X".
Tipo di sanguinamento: differente rispetto all'emofilia congenita.
Entità del sanguinamento: per lo più importante con anemia, talora drammatico.
Trasfusione di globuli rossi concentrati: spesso necessaria e ripetuta.
Trasfusione di plasma: "alle dosi raccomandate" inefficace (APTT non corregge).

Terapia antiemorragica
Terapia immunosoppressiva

Ricercare patologie sottostanti, anche quelle neoplastiche!



Grazie per l'attenzione