ACQUIRED HEMOPHILIA - CLINICAL COURSE AND TREATMENT OUTCOMES IN 25 PATIENTS

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OBJECTIVES

- Acquired hemophilia is a rare disorder caused by auto-antibodies against FVIII with a typical occurrence in elderly patients and serious bleeding manifestation in 87% of patients.
- Until recently a high mortality of syndrome up to 22% was reported.
- The syndrome is associated with autoimmune diseases, neoplasia, pregnancy and drug reactions, however, in about 50% of the cases no underlying disorder can be identified.
- A prompt diagnosis of disorder is essential for the appropriate management.
- In case of bleeding the first choice treatment are bypassing agents: recombinant FVIIa and activated prothrombin complex (aPCC-FEIBA)
- To eradicate FVIII inhibitor several immunosuppressive approaches have been proposed.

AIM OF STUDY AND METHODS

- Aim of study: to evaluate the etiology, clinical course, treatment of bleeding and success of inhibitor eradication in all concecutive patients with acquired hemophilia treated in our centre between 1996-2011.
- FVIII inhibitor was measured using Bethesda method.
- Major and/or surgical bleeds are treated initially with rFVIIa in standard dosing regimen (2-3 days), when prolonged correction of hemostasis is required, the treatment continues by standard administration of FEIBA.
- For moderate bleeds either rFVIIa or FEIBA are used in standard doses.
- Prednisone (Pred) and cyclophosphamide (CTX) were the first line therapy for inhibitor eradication, 4 patients received immune tolerance induction (ITI): FVIII+ M-Pred +CTX.
- Combined immunosupression (CVP), mycophenolate mofetil (MM), cyclosporine A (CsA) and most recently rituximab (Ritux) were employed as the second line therapy.

RESULTS

Tab. 1 Acquired hemophilia– Patients characteristics

Pts with acquired hemophilia (n)	25
M / F (n)	11 / 14
Age at diagnosis (years)*	70 (23 - 96)
FVIII:C (IU/dL)*	0.9 (0.2 – 8.0)
Inhibitor titre (BU/mL)*	32 (6 – 1260)
Bleeding present at diagnosis(n pats/%)	25 (100%)
traumatic/surgical bleeds	6 (24%)
major bleeding	5 (20%)
moderate bleeding	4 (16%)
mild bleeding, therapy not required	10 (40%)
Hemoglobin at diagnosis (g/dL)*	8.0 (4.4-10.0)

*values expressed in medians(range)

Fig.1 Etiology of acquired hemophilia (n=25)

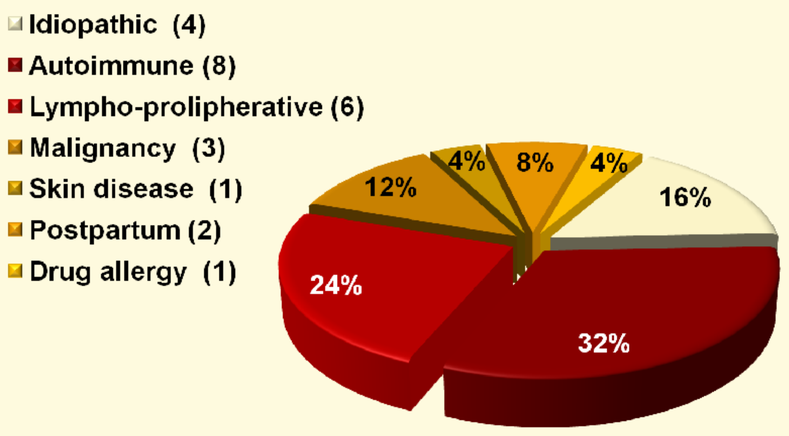
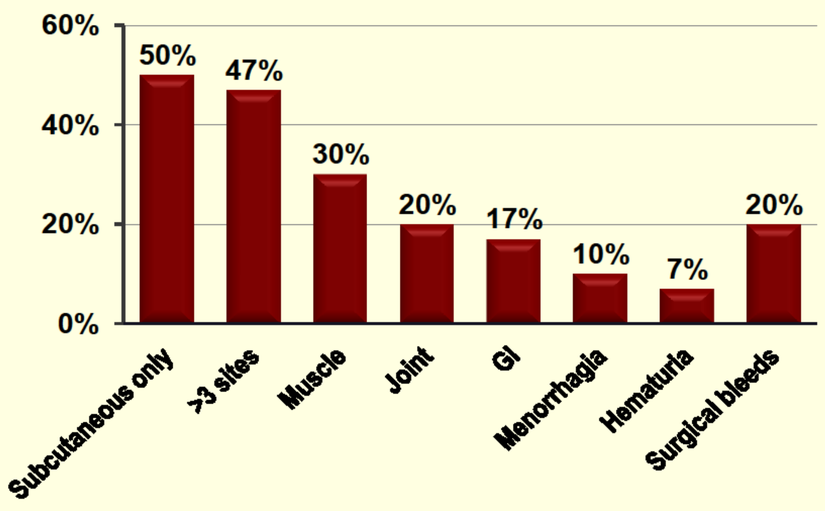


Fig.2 Types of bleeding in acquired hemophilia



Tab.2 Underlying disease, inhibitor titre and the outcomes of the consecutive inhibitor eradication regimens

P	Age at dg	Underlying disease	Inhibitormaxim. (BU/ml)	Inhibitor eradication regimen	CR (time to-wks)	Relapse (time to-mths)	Follow up (mths)	Outcome
1	71	CLL	8	Pred, CTX	2	3*	72	CR#
2	96	Idiopathic	131	Pred	3	3	6m	Relapse$
3	22	Postpartum	32	Pred	12		132	CR
4	70	Myeloma	60	Pred, CTX ,CVP,CsA	No		24	Inhibitor $
5	62	Colitis ulcerosa	30	Pred, CTX	13	2*	72	CR
6	41	Psoriasis	12	Pred, CTX ,ITI, CVP	No		36	Inhibitor $
7	68	Lung Ca	55	Pred	No		1m	Inhibitor $
8	52	Pancreas Ca	890	Pred, CTX, ITI	No		12	Inhibitor $
9	70	Ly-prolipherative	50	Pred, CTX	4		36	CR#
10	77	Idiopatic	15	Pred	5		36	CR#
11	67	Asthma	44	Pred, ITI, CTX	8		78	CR
12	75	B-NHL	7	Pred	2	3*	16	CR$
13	85	Renal failure	6	Pred	1	7*	24	CR#
14	54	Adenoma	1260	Pred,CTX ,CVP,CsA, MM, Ritux	6 yrs		84	CR
15	42	MGUS	10	Pred	3		120	CR
16	73	Skin mycosis	116	Pred, CTX	5		2	CR
17	36	Postpartum	42	Pred	6		24	CR
18	64	Autoimmune dis.	8	Pred	3		132	CR#
19	68	Rheum. artritis	300	Pred, CTX,ITI, CVP, CsA	5 yrs		132	CR
20	83	Autoimmune dis.	71	Pred, CTX	4		2	CR$
21	62	Dermatomyositis	7	Pred	3	7*	120	CR
22	71	MGUS λ	33	Pred, CTX	7		12	CR
23	65	Drug alergy	35	Pred, CTX	8		130	CR#
24	73	Asthma,RA	28	Pred	3		36	CR
25	75	Idiopatic	18	Pred	2		60	CR

Treatment regime in red characters: therapy resulting in complete remission (CR)
*: second remission achieved in 2- 6 weeks
: lost from follow up in the complete remission
$: death due to underlying disease

Pred: prednisone; CTX: cyclophosphamide; CVP: CTX, vincristine, prednisone
ITI: immune tolerantion induction with low dose FVIII + Methylprednisolone + CTX;
CsA:cyclosporine A; MM: Mycophenonale mofetil, Ritux: rituximab- anti CD20

Fig. 3 Therapy of 66 bleedings in 17 pats: Duration, use & consumption of bypassing agents per bleeding episode

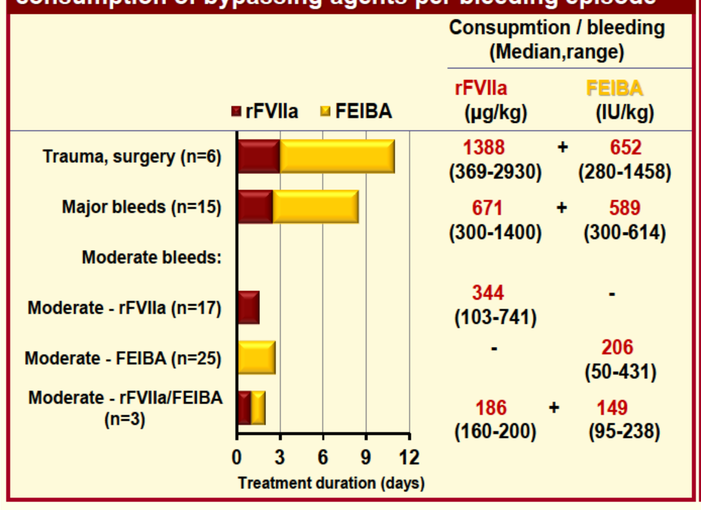
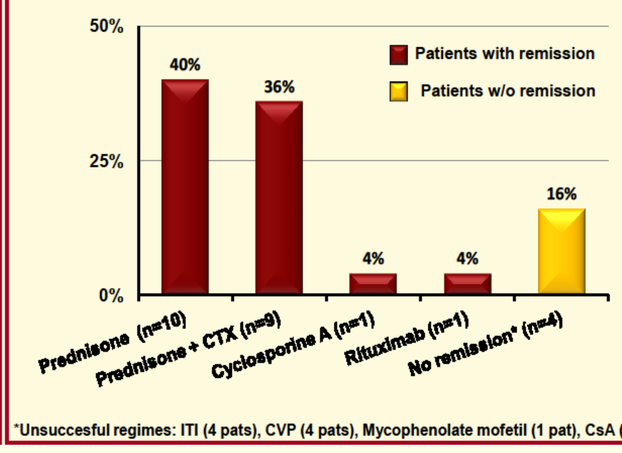


Fig.4 Proportion of patients with succesful inhibitor eradication according to immunosuppresive regimens (Overal success: 21/25 = 84%)



*Unsuccesful regimes: ITI (4 pats), CVP (4 pats), Mycophenolate mofetil (1 pat), CsA (1pat)

DISCUSSION

- Majority of pts in our cohort (84%) had underlying disease with possible association with acquired hemophilia.
- Serious bleeding at diagnosis resulted in severe anemia in most pts: Hbg 8.0 (4.4-1.0)g/dL.
- Seventeen of 25 (68%) pts required hemostatic therapy for a total of 66 bleeding episodes. Duration of treatment (median,range) for 6 surgical,15 major and 45 moderate bleedings was 10,8 (7-18), 8 (3-12) and 2 (1-5) days, respectively, with products consumption shown in Fig 3.
- In major/surgical bleeds we start with a standard treatment with rFVIIa for 2-3 days, continuing therapy with aPCC (FEIBA) when prolonged hemostatic correction is required.
- Both bypassing agents are highly effective and safe, we have not observed any death due to the bleeding, nor thrombotic complications of therapy.
- Inhibitor was eradicated in 21/84% pts: 19 remissions (90%) were achieved by prednisone and CTX in a median time 3.5 wks (range 1-13 wks). In one and one patient inhibitor persisting for 6 and 5 yrs was eradicated with CsA therapy administered for rheumathoid arthritis and by two courses of rituximab, respectively.
- Inhibitor relapsed in 6/21 (29%) pts with remission, in 5 pats a second remission was succesfully reinduced with prednisone therapy.
- Median follow up in the whole group was 36 mths and in patients with remission 72 mths (range 1mth-11 years). Several patients were lost from the follow up due to an advanced age.

CONCLUSION

- Effective bypassing agents and a high rate of succesful inhibitor eradication changed previously poor prognosis of patients with acquired hemophilia.
- Nevertheless, the management of this disorder is challenging due to:
  - mostly the very old patients with serious comorbidities are affected.
  - the enormous demands on treatment, unusual for this age population.

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