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# Acquired haemophilia A in southern Switzerland from 2013 to 2019: a case series

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## Summary

AIMS OF THE STUDY: Acquired haemophilia A is a rare disease with an annual incidence of 1.48 per million. Based on clinical observations, we suspect a higher incidence in southern Switzerland, and aimed at providing local epidemiological data, and clinical information regarding diagnosis, treatment and outcome in our region.

METHODS: All adult patients with acquired haemophilia A treated between 2013 and 2019 in our facility were included in the present retrospective analysis.

RESULTS: We treated 11 patients with acquired haemophilia A between 2013 and 2019, resulting in an annual incidence of 4.5 per million (95% confidence interval [CI] 0–9.0). Median delay from first symptoms to diagnosis was 4.5 days, and the median age at diagnosis was 79 years (range 23–87). Possible causative conditions were: pregnancy (n = 1), polyarteritis nodosa (n = 1), myelodysplastic syndrome (n = 1), chronic human immunodeficiency virus (HIV) (n = 1), and HIV postexposure prophylaxis (n = 1). In five patients no underlying or associated condition was identified. Median activated partial thromboplastin time (aPTT)) at baseline was 79 seconds (65–117; ref. value <38 sec), and FVIII:C 2.15% (<1–3.75%). A FVIII:C <1% was present in 4/10 patients. Median FVIII-inhibitor titre was 10.3 BU/ml (2.4–75.0 BU/ml). All patients had bleeding symptoms, 5/10 patients had major bleedings, and 7/10 patients were treated with bypassing agents. All patients received corticosteroids; 7/10 patients received immunosuppressive combination therapy. FVIIIlevels of ≥50% were achieved after a median of 40 days (8–62). One patient had a severe immunosuppressive therapy-related infection. An 87-years-old woman died for reasons not related to acquired haemophilia A or immunosuppressive therapy.

CONCLUSI ONS: Acquired haemophilia A is a rare disease, but manageable despite the advanced patient age and comorbidities. Its incidence in Southern Switzerland is higher than previously suspected.

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## Introduction

Acquired haemophilia A is a rare autoimmune disorder with a reported annual incidence of 1.48 patients per 1 million. Mortality of acquired haemophilia A can be as high as 33%, with deaths directly related to bleeds ranging from 3%–9% [1–4]. Infections related to immunosuppressive therapy (IST) and underlying conditions make up for the rest of the mortality [1, 2, 4–6]. There are two peaks in onset of acquired haemophilia A, one in younger women aged 20–40 years, mostly related to pregnancy, and a second associated with age (>65 years) [7–9]. The reasons for antibody development against coagulation factor VIII (FVIII) are still largely unknown [10, 11]. There is an association with certain HLA class II alleles, with single nucleotide polymorphisms of the CTLA-4 gene, as well as with mutations in the FVIII gene [12, 13].Neutralising anti-factor VIII (anti-FVIII) antibodies in patients with acquired haemophilia A are primarily directed to the A2, C1 and C2 domains [14]. Anti-factor VIII antibodies of the IgA subtype are associated with a higher rate of recurrence [15]. About half of the patients have no identifiable trigger ("idiopathic acquired haemophilia A"), whereas the other half of the patients have underlying or associated neoplasia, autoimmune diseases or a history of exposure to certain drugs at the time of haemophilia diagnosis [1, 2, 4, 16–20]. The bleeding pattern in patients with acquired haemophilia A is different from that in patients with severe congenital haemophilia A. Joint bleedings are rare, but large skin haematomas, gastrointestinal and urogenital as well as muscle and retroperitoneal bleedings are common (figure 1) [4, 21]. Overall, the bleeding phenotype seems to be more severe in acquired than in congenital haemophilia A, and is possibly related to age, concomitant medication and the specificity of the anti-FVIII antibody [22].

Once acquired haemophilia A is suspected, the diagnostic process is straightforward [4]. The prothrombin time (Quick/INR) is normal and patients have a markedly prolonged activated partial thromboplastin time (aPTT). In this situation aPTT mixing studies, which can be done in non-specialised routine laboratories, are an important first diagnostic step (fig. 2) [23–26]. Further analyses include measurement of FVIII coagulation activity (FVIII:C) and confirmation of the FVIII inhibitor in specialised laboratories [8].

Up to one third of the patients will have spontaneous remission of acquired haemophilia A, but given the devastating consequences of severe haemorrhage, most experts agree that immediate treatment is necessary for all patients [8, 27]. There are three major pillars of acquired haemophilia A treatment. First, unnecessary interventions must be avoided, including venous punctures, frequent blood pressure measurements, endoscopy or surgery. Second, haemorrhage should be controlled using one of the two currently available FVIII bypassing agents, recombinant activated factor VII (rFVIIa; NovoSeven®) and activated prothrombin complex concentrate (aPCC; FEIBA®), or recombinant porcine FVIII susoctocog alfa (rpFVIII; Obizur®) [8].Due to inactivation by circulating anti-FVIII antibodies, conventional FVIII concentrates are generally not effective and should be avoided. Third, immunosuppressive treatment should be started immediately to halt autoantibody production. The backbone of immunosuppressive treatment are corticosteroids, although timely addition of the anti-CD20 antibody rituximab is now recommended, especially in the case of low FVIII activity (<1%), high inhibitor titres (>20 Bethesda units (BU)/ml) or corticosteroid intolerance [8]. Cyclophosphamide can be added as a corticosteroid-sparing agent, or in case of treatment failure [5].

We report incidence, clinical presentation and outcome of acquired haemophilia A diagnosed in Southern Switzerland between 2013 and 2019.

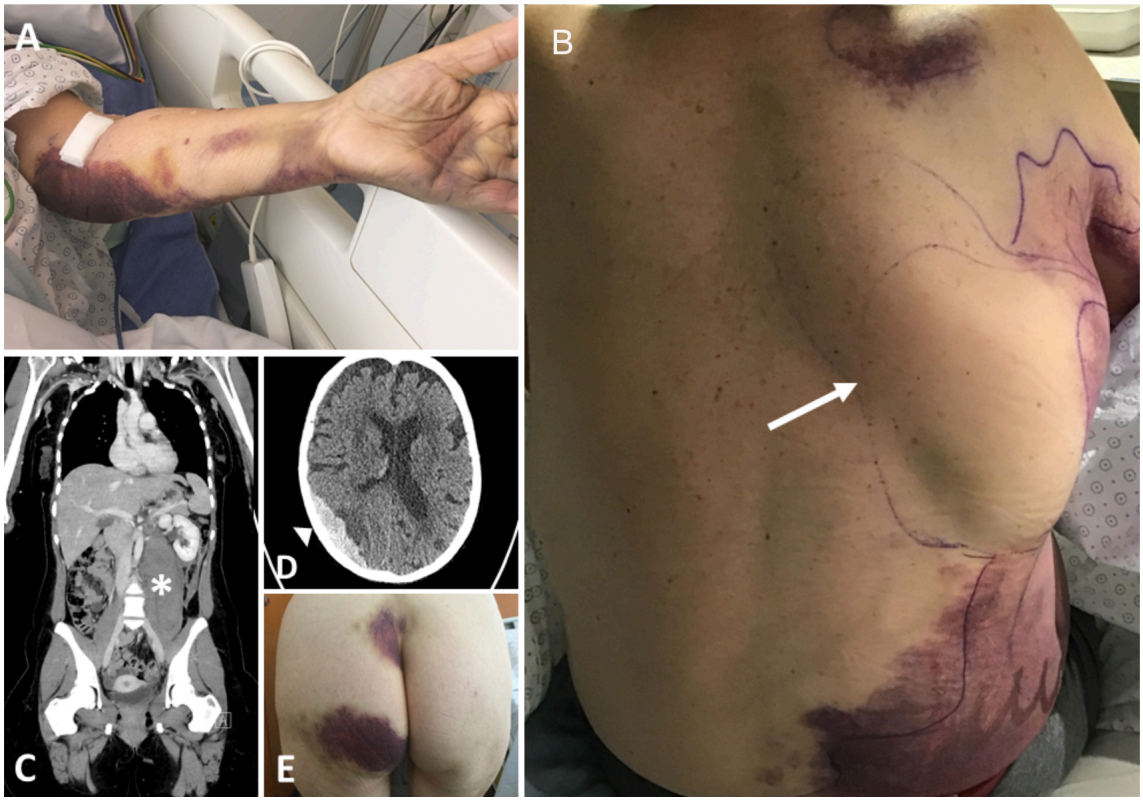
## Patients and methods

Adult patients diagnosed with acquired haemophilia A at the Ente Ospedaliero Cantonale (EOC) between 2013 and 2019 were included. The end of follow-up was 31 March 2020. Clinical data were extracted retrospectively from the electronic patient chart. Bleeding was graded according to the current International Society on Thrombosis and Haemostasis (ISTH) criteria [28].

### Hospital and laboratory setting

Ente Ospedaliero Cantonale is the only public healthcare provider in the Italian speaking part of Southern Switzerland (Ticino), a region with 353,500 inhabitants. It is a tertiary care referral centre with 903 beds and 370,000 outpatient visits per year and consists of five small- to medium-sized acute-care hospitals, two chronic-care facilities and one rehabilitation centre. The five acute care facilities are geographically separated, and each has its own laboratory facility, offering basic coagulation assays including prothrombin time, activated partial thromboplastin time, fibrinogen and d-dimer measurement. Specialised co-

**Figure 1:** Bleeding pattern in patients with acquired haemophilia A; (A) subcutaneous bleeding after venipuncture (patient 9). (B) large spontaneous bruises and bleeding into the latissimus dorsi muscle (arrow; patient 8). (C) spontaneous retroperitoneal bleeding in the psoas muscle (asterisk; patient 3); (D) subdural haematoma following frequent falls while on direct oral anticoagulant therapy (arrowhead; patient 4); (E) large skin haematomas on the backside under low-dose heparin therapy (patient 5).



agulation testing is centralised in two main laboratory facilities.

### Coagulation assays

The coagulation tests are performed using citrated plasma (0.109 M/3.2% Vacutainer tubes from Becton Dickinson). Prothrombin time (ref. value Quick 70–130%, ReadiPlasTin®, HemosIL), aPTT (ref. value 25–37 seconds; SynthASil®, HemosIL), coagulation factor VIII (ref. value 50–150%, SynthASil®, HemosIL), and anti-Xa activity (Liquid Anti-Xa®, HemosIL) are determined on the ACL TOP 350 and ACL TOP 550 coagulometers (Axonlab). Normal pooled plasma is used for aPTT mixing studies. The mixing studies are performed by adding to the patient's plasma an equal volume of NPP (1:2 mix). aPTT in patient plasma, in normal pooled plasma and in the 1:2 mix is measured immediately and after a two-hour incubation at 37 °C in a water bath (fig. 2). The Rosner index at 2 hours (RI = [aPTT mix – aPTT NPP) / aPTT patient × 100]) is calculated automatically. For patients with an RI ≥11% (inhibitor possible) a senior haematologist is informed by the laboratory technician, whereas in patients with an RI <11% (inhibitor unlikely) only a consultation with a haematologist is recommended. The presence of a FVIII inhibitor is assessed in a modified Nijmegen assay on an Atellica COAG 360 (Siemens, Germany).

All patients signed a written informed consent for publication, and the competent local ethical committee waived the need for formal review board approval of the study (Req-2019-00726).

### Statistical analysis

Statistical analyses were performed with Microsoft Excel Software or R statistics (version 4.1.3). Baseline characteristics are displayed as median with range and interquartile range (IQR) or absolute numbers with percentages, as appropriate. For the incidence calculations, the cases of acquired haemophilia A were used as numerators and the total population of the Ticino as denominator. The population data was by the Swiss Federal Statistical Office. The mean annual incidence rate and the 95% confidence interval [CI]was calculated over the whole 7-year observation period.

## Results

### Incidence and underlying diseases

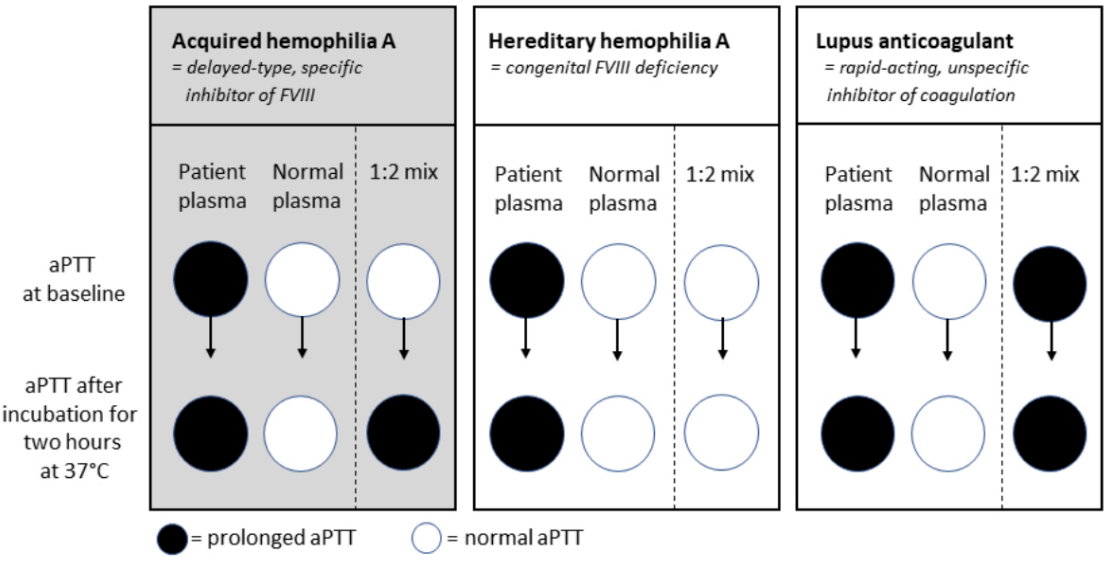
Eleven cases of acquired haemophilia A were diagnosed between 2013 and 2019, resulting in an annual incidence of 4.5 cases per 1 million inhabitants (95% CI 0–9.0). One patient did not give consent to participate, and 10 patients were included in the final analysis.

Median age at diagnosis was 79 years (range 23–87), 7/10 patients were female (table 1). One patient had acquired haemophilia A related to pregnancy; a 23-year-old female healthcare worker developed acquired haemophilia A after HIV postexposure prophylaxis, one patient had polyarteritis nodosa, one patient hat myelodysplastic syndrome, and one patient chronic HIV infection with antiretroviral treatment. No associated or underlying condition was identified in the other five patients.

### Coagulation tests

Median aPTT at baseline was 79 seconds (IQR 65–117); Quick/INR was abnormal in one patient receiving vitamin K antagonists (table 2). Median Rosner index at 2 hours was 30 (IQR 26.6–41.0), median FVIII:C 2.15% (IQR

**Figure 2:** Typical examples of activated partial thromboplastin time (aPTT) mixing studies for patients with normal prothrombin time (Quick/INR) and prolonged aPTT at baseline. Patients with acquired haemophilia A have an increased bleeding risk, and a prolonged aPTT at baseline, which normalizes when adding normal plasma (1:2 mix), but increases after 2 hour incubation at 37 °C due to a delayed-type inhibitor; Patients with hereditary haemophilia A have an increased bleeding risk, and a prolonged aPTT at baseline, which normalizes when adding normal plasma (1:2 mix), and remains normal after 2 hour incubation at 37 °C; Patients with positive lupus anticoagulant can have an increased risk for thrombosis, and have a prolonged aPTT, which does not normalize when adding normal plasma (1:2 mix), and stays prolonged after 2 hour incubation at 37 °C due to a rapid-acting inhibitor.



<1–3.75%). A FVIII:C <1% was present in 4/10 patients. Median FVIII inhibitor was 10.3 BU/ml (IQR 2.4–75.0 BU/ml), and 4/10 patients had a titre >20 BU/ml.

### Bleeding manifestations and treatment of bleeds

In half of the patients, the first haemorrhagic manifestation was a major bleeding (gynaecological, muscular, intracranial, cutaneous); two out of these five events were unprovoked (table 1). The remaining five patients had minor, mostly unprovoked mucocutaneous bleedings. FVIII bypassing agents were given in 7/10 patients (table 2), and most patients received first rFVIIa, and switched to prothrombin complex concentrate (aPCC) during the course of the disease. No patient was treated with recombinant porcine FVIII (rpFVIII). Red blood cell transfusions were necessary in 8/10 patients.

### Immunosuppressive therapy

All patients were treated with corticosteroids, seven of them received in addition rituximab and/or cyclophos-

**Table 1:**
Patient baseline characteristics.

| Patient-ID | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | Median (IQR) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Gender | f | m | f | f | f | f | f | m | f | m | |
| Age (years) | 41 | 68 | 23 | 87 | 77 | 83 | 82 | 71 | 84 | 87 | 79 (69–84) |
| Year of diagnosis | 2013 | 2016 | 2017 | 2017 | 2017 | 2017 | 2018 | 2019 | 2019 | 2019 | |
| Comorbidities | – | Ischaemic cardiopathy, DM, aHT | HIV-PEP | MDS | Ischaemic cardiopathy | aHT | Ischaemic cardiopathy | Polyarteritis nodosa | DM, aHT | Ischaemic cardiopathy, aortic valve stenosis | |
| Anti-aggregation / anticoagulation | – | ASS | – | DOAC | Heparin | – | ASS | VKA | – | ASS | |
| AHA trigger | Pregnancy | HIV (on ART) | Idiopathic (PEP) | MDS | Idiopathic | Idiopathic | Idiopathic | PAN | Idiopathic | Idiopathic | |
| Diagnostic delay (days) | 5 | 22 | 0 | 4 | 1 | 89 | 9 | 4 | 0 | 14 | 4.5 (2–13) |
| Type of bleeding | Obstetrical | Cutaneous | Cutaneous Muscular | CutaneousCNS | Cutaneous | Muco-cutaneous | Cutaneous | Cutaneous Muscular | Cutaneous | Cutaneous | |
| Cause of bleeding | Iatrogenic | Minor Trauma | Major Trauma | Minor Trauma | Spontaneous | Spontaneous | Spontaneous | Spontaneous | Minor Trauma | Spontaneous | |
| ISTH bleeding grade | Major | Minor | Major | Major | Minor | Minor | Minor | Major | Minor | Major | |

F = female; m = male; PEP = postexposure prophylaxis; DM = diabetes mellitus; aHT = arterial hypertension; ASS = acetylsalicylic acid; VKA = vitamin K antagonist; DOAC = direct oral anticoagulant; AHA = autoimmune haemophilia A; PAN = polyarteritis nodosa; ART = antiretroviral therapy; MDS = myelodysplastic syndrome; CNS = central nervous system; IQR = interquartile range; ISTH = International Society on Thrombosis and Hemostasis.

**Table 2:**
Coagulation tests at diagnosis and during follow-up, coagulation factor consumption and transfusion of blood products.

| Patient-ID | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | Median (IQR) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Baseline** | | | | | | | | | | | |
| aPTT (sec) | 64 | 118 | 49 | 112 | 44 | 76 | 67 | 200 | 200 | 82 | *79 (65–117)* |
| aPTT mix 1:2 (sec) | 34 | 45 | 31 | 51 | 37 | 37 | 37 | 121 | 47 | 41 | *39 (37–47)* |
| **After 2 h at 37 °C** | | | | | | | | | | | |
| aPTT (sec) | 74 | 108 | 68 | 118 | 68 | 82 | 84 | 172 | 200 | 89 | *87 (76–116)* |
| aPTT mix 1:2 (sec) | 55 | 75 | 47 | 95 | 45 | 51 | 54 | 201 | 85 | 60 | *58 (52–83)* |
| Rosner index (2 h) | 41.9 | 38.9 | 23.5 | 46.6 | 16.2 | 26.8 | 28.6 | 98.3 | 26.5 | 31.5 | *30 (26.6–41)* |
| FVIII:C (%) | 2.3 | <1 | 10 | <1 | 11 | 4 | 3 | <1 | <1 | 2 | *2.15(<1–3.75)* |
| FVIII-Inhibitor (BU) | 1.8 | 103 | 0.8 | 53 | 1.6 | 8.4 | 2.4 | 330 | 75 | 10.3 | *10.3 (2.4–75)* |
| rFVIIa (mg/kg) | 3.9 | 0.3 | 0.1 | 0 | 0 | 0 | 0 | 2.5 | 0.1 | 0.2 | *0.1 (0–0.3)* |
| aPCC (IU/kg) | 0 | 1611 | 744 | 1750 | 0 | 0 | 0 | 1703 | 665 | 53 | *359 (0–1395)* |
| FFP (U) | 6 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | *0* |
| RBC (U) | 9 | 2 | 4 | 20 | 2 | 0 | 0 | 9 | 1 | 2 | *2 (1–8)* |
| Platelet transfusion (U) | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | *0* |
| Immunosuppression | P / C | P / C | P / R / C | P / R | P | P | P | P / R / C / IA | P / R | P / R | |
| Prednisone (days) | 151 | 157 | 907 | 64 | 74 | 132 | 203 | ongoing | 108 | ongoing | |
| **Time to FVIII:C** | | | | | | | | | | | |
| ≥5% (days) | 1 | 31 | *NA* | 28 | *NA* | 5 | 2 | 11 | 7 | 2 | *6 (2–15)* |
| ≥50% (days) | 39 | 52 | 51 | 46 | 8 | 41 | 14 | 62 | 24 | 18 | *40 (20–50)* |

aPTT = activated partial thromboplastin time; mix 1:2 = mix of patient plasma and standard plasma (50% each); 2h-aPTT = aPTT after 2 hours of incubation at 37 °C; Rosner index = (aPTT mix – aPTT standard) / aPTT patient × 100; BU = Bethesda units; rFVIIa = Recombinant factor VIIa (rFVIIa; NovoSeven®); aPCC = activated prothrombin complex concentrate (FEIBA®); FFP = fresh frozen plasma; IQR = interquartile range; RBC = red blood cell concentrate; U = units; P = prednisone; R = rituximab; C = cyclophosphamide; IA = immunoadsorption

phamide (table 2). One patient was treated with immunoadsorption of the FVIII inhibitor.

### Disease course and side effects

FVIII:C levels ≥50% were achieved after a median of 40 days (range 8–62 days) (table 2). One patient had asymptomatic disease recurrence one month after corticosteroid suspension. Four patients had side effects of corticosteroid treatment (arterial hypertension, hyperglycaemia, insomnia, agitation, and myopathy) and one patient had erysipelas during rituximab-induced neutropenia. One 87-year-old female patient (tables 1 and 2, patient 4) died 17 months after the diagnosis of acquired haemophilia A of heart failure, cause of death was unrelated to the haemophilia or immunosuppressive therapy.

## Discussion

The annual incidence of acquired haemophilia A in Ticino between 2013 and 2019 was 4.5 cases per million inhabitants. Although the low absolute number of in our study leads to uncertainty regarding the incidence estimates, acquired haemophilia A seems to be more frequent in Southern Switzerland than in the UK (1.48 cases per million per year), and more in line with recent data reported by German colleagues (5–6 cases per million per year) [1, 29]. Our data are likely incomplete, thus underestimating the true incidence, as only patients with acquired haemophilia A referred to our public hospital could be included. In 2018, we implemented an acquired haemophilia A screening algorithm for all patients with a prolonged aPTT, and a normal prothrombin time on a first occasion.

With a median age of 79 years in Southern Switzerland, and 74–78 years in large registries, acquired haemophilia A is clearly a disease of the elderly [1, 4]. The late onset of disease is challenging, as many patients suffer from comorbidities at the time of haemophilia diagnosis [30, 31]. Anti-platelet therapy or anticoagulation are prevalent in this age group and expose the patients to an additional bleeding risk at the onset of acquired haemophilia A. Conversely, the discontinuation of anti-platelet therapy or anticoagulation together with the use of haemostatic bypassing agents exposes the patients to an elevated thrombotic risk. Diabetes mellitus is a concern, as corticosteroids will lead to difficult-to-control blood glucose levels. In our cohort of ten patients, four had coronary heart disease and two diabetes mellitus.

We identified possible triggers for FVIII inhibitor development in 5/10 patients. However, with the exception of the one patient with acquired haemophilia A in the peripartum period, the other four conditions could be causative as well as coincidental.

The median diagnostic delay from first symptoms prior to admission to diagnosis was 4.5 days, which is similar to the three days reported in larger studies [4]. Most common presentations at diagnosis were large skin haematomas with or without trauma, and a markedly prolonged activated partial thromboplastin time of more than twice the upper limit of normal, with a typical delayed-type inhibitor in the aPTT mixing studies. All of our patients had bleedings, but no patient died due to haemorrhagic complications, which is in line with the bleeding mortality of 3% observed in the EACH registry [4]. The majority of our patients needed treatment with FVIII bypassing agents. The treatments of choice in our institution are rFVIIa and aPCC (prothrombin complex concentrate) [1, 32, 33].

We did not use the recombinant porcine FVIII (rpFVIII), susoctocog alfa or the bispecific antibody emicizumab in our patients, as both drugs were not yet reimbursed for this indication in Switzerland. Susoctocog alfa is a therapeutic alternative, but cross-reacting antibodies may reduce FVIII recovery, and antibody detection and frequent FVIII measurements with a suitable laboratory test are mandatory [8, 34, 35]. Emicizumab, a recombinant, humanised bispecific antibody with FVIII-like activity has been used in a few cases of acquired haemophilia A so far, but no high-quality data in acquired haemophilia A is available [36, 37].

All of our patients received immunosuppressive treatment. Reasons for initiating immunosuppressive combination therapy were low FVIII:C, high inhibitor titre, major bleeding, and corticosteroid-related side effects. Initially, and in accordance with the GTH-AH 2010/01 study protocol cyclophosphamide was our preferred second-line immunosuppressive therapy [38]. In 2019, we changed our policy by adding rituximab early in the treatment process, if a poor response to corticosteroids was predicted (FVIII:C <1%, and/or inhibitor titre >20 BU/ml), or if tolerability of corticosteroid therapy was a concern [8]. Only one of our patients experienced a severe infectious complication, and no patient died because of immunosuppressive therapy. FVIII:C restored to values >50% within a median of 40 days, which is in line with previous reports using similar immunosuppressive therapy approaches, but shorter than reduced-intensity schemes [38, 39]. Our relatively small patient cohort does not allow for statistical subgroup analysis, but individuals with low initial FVIII activity (<1%), and a high FVIII inhibitor titre, had delayed FVIII normalisation and higher consumption of bypassing agent, than patients with an initial FVIII:C ≥1%. All patients achieved complete remission (normal FVIII activity, clearance of the FVIII inhibitor), and only one patient experienced an asymptomatic relapse.

Our present report has limitations, mainly the relatively short observation period of seven years, which might be subject to a sampling bias, the low patient number, and the retrospective data collection, that does not allow for more detailed statistical analysis. Nevertheless, our data are representative for the disease and in line with data obtained from large registries (table S1) [1, 4, 5, 38, 40]. Also, the true incidence of acquired haemophilia A in Ticino is very likely underestimated, as our analysis includes only the patients treated in the public hospitals.

In conclusion, we report an annual incidence of acquired haemophilia A of 4.5 cases per million inhabitants in our region. The outcome of acquired haemophilia A was favourable despite the advanced age of the patients.

*Parts of this work have been presented at the Annual Meeting of the Society of Thrombosis and Hemostasis Research (GTH) 2020, Bremen, Germany.*

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**Authorship contributions:** AR and BG designed the study; BG, AV, AR and FN collected and analysed data, BG and AR wrote the first draft of the manuscript; AR and BG performed statistical analyses; all authors critically read, discussed and corrected the manuscript.

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**Potential competing interests**
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# Appendix

**Table S1:**
Comparison of large collections of patients with acquired haemophilia A.

| Reference | Inclusion period/region | Number of patients / study design | Incidence per year | Female sex | Median age, years (range) | Days to diagnosis, (range) | idiopathic | Median FVIII:C (%) (IQR) | Median FVIII -inhibitor, (BU/ml) (IQR) | Major bleeding | Hemostatic agents needed | IST | CR / time to remission (days) | Mortality | Relapse |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Collins et al. 2007 [41] | 2001–2003 UK | 172 / retrospective multicentre questionnaire | 1.48/mio | 57% | 78 (2–98) | ND | 63% | 3 (1.7–7) | 13 (4–28) | 66% | 67% | 95% | 71%/57[a] | 9.1% due to bleeding | 20% |
| Knoebl et al. (EACH2) [42] | 2003–2008 Europe | 501 / prospective multicentre registry | ND | 47% | 74 (61–80) | 3 (0–12) | 52% | 2 (1–5) | 12.8 (4.3–42.4) | 70.3% | 70% | 95% | 72.6%/ND[b] | 20% (in total), 3% due to bleeding | ND |
| Borg et al. 2013 (SACHA) [43] | 2001–2005 France | 82 / prospective multicentre registry | ND | 39% | 77 (25–103) | ND | 55% | 2 (<1–30) | 16 (1–2800) | 35% | 46% | 88% | 61% /ND | 33% (in total), 3.5% due to bleeding, 12% treatment related | 0% at 1 year |
| Jayakar et al. 2018 [44] | 1990–2016 Canada | 40 / retrospective single centre | ND | 32% | 68 (ND) | ND | 63% | ND | ND | 40% | 74% | 100% | 73%/ND | 4.5% due to bleeding | ND |
| Huang et al. 2015 [45] | 1987–2010 Taiwan | 65 / retrospective two centres | ND | 35% | 64 (18-94) | ND | 52% | 65% (<1% FVIII:C), 35% mean 3.8 (1.1–17)% | 19.4 (0.7–2414) | 14% | ND | 86% | 60%/16 weeks | 29% due to bleeding, 20% treatment related | 12% |
| Ruberti et al. 2023 (this article) | 2013–2019 Switzerland | 10 / retrospective single centre | 4.5/mio | 70% | 79 (23–87) | 4.5 (2–13) | 50% | 2.15 (<1–3.75) | 10.3 (2.4–75) | 50% | 70% | 100% | 100%/40[c] | 10% (in total), 0% due to bleeding | 10% |

FVIII:C: FVIII activity; BU = Bethesda units; IST: Immunosuppressive treatment; IQR: interquartile range; CR: complete remission; ND: data not reported.

[a] normal FVIII:C, FVIII inhibitor undetectable and immunosuppression stopped.

[b] FVIII:C >70%, FVIII inhibitor undetectable and no replacement therapy.

[c] sustained FVIII:C >50%.