Clinical features and outcome of acquired haemophilia A
Interim analysis of the Düsseldorf Study*§

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Keywords
Acquired haemophilia A, autoantibodies, morbidity, mortality, underlying disorder

Summary
We have performed a monocenter study on 29 consecutive patients with acquired haemophilia A who were referred for diagnosis and treatment to the Düsseldorf Haemophilia Comprehensive Care Center between March 2001 and February 2010. Patients, methods: 18 men (age: 44–86 years) and 11 women (age: 20–83 years). For laboratory evaluation, a standardized staged protocol of aPTT, FVIII:C activity and concentration, mixing studies with patient and normal plasma, and quantification of inhibitor titre (Bethesda assay) was used. Diagnostic work-up included elaborate examinations for any underlying disease. Results: In 18 (62%) of the 29 patients with acquired haemophilia A, an underlying disorder was identified, including 9 patients with respiratory diseases (31%), 7 patients with autoimmune disorders (24%), one with malignancy, and one with postpartum state, while in 11 patients (38%) acquired haemophilia A remained idiopathic. Haemotherapy of bleeding, suppression or elimination of the inhibitor, and induction of immunotolerance to endogenous FVIII:C were performed according to a treatment algorithm. Predefined clinical endpoints were control of bleeding, eradication of the inhibitor, complete or partial remission (CR, PR), relapse, or early death (≤30 days). Of the 29 patients in total, 22 individuals achieved CR (76%), three had PR, one relapsed, and three died within 30 days (one of acute myocardial infarction while on antihaemorrhagic treatment, one of sepsis while on immunosuppression due to active acquired haemophilia A, one of lung bleeding in association with pre-existing pulmonary sarcoidosis). Conclusion: This monocenter study demonstrates that control of life-threatening bleeding, eradication of the inhibitor, and induction of tolerance to endogenous FVIII have significantly improved the clinical outcome of acquired haemophilia A. Our data also suggest a shift in underlying disorders associated with acquired haemophilia A, whereby, in comparison to published studies, a relative increase in the proportion of patients with respiratory diseases is present.

Schlüsselwörter
Erworbene Hemmkörperhämophilie A, Autoantikörper, Morbidität, Mortalität, Grundkrankung

Zusammenfassung

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Klinische Erscheinungsbilder und Ergebnisse bei erworbener Hemmkörperhämophilie A: Zwischenauswertung der Düsseldorfer Studie*§

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* Dedicated to Prof. Peter Hanfland, Bonn, on the occasion of his 70th birthday.
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Acquired haemophilia A is a rare but significant haemostatic disorder caused by autoantibody inhibitors against factor VIII coagulant protein (FVIII:C). The incidence of acquired haemophilia A has been estimated at about 1 to 4 cases per million per year (4, 5, 7). No such data are available of acquired haemophilia B but its annual incidence is even less frequent. Acquired haemophilia A affects patients with (7)

- pre-existing autoimmune disorders (such as systemic lupus erythematosus, rheumatoid arthritis, Sjögren syndrome, myasthenia gravis, multiple sclerosis, hyperthyroidism, Goodpasture syndrome, and others),
- underlying haematologic malignancies or solid cancers,
- concomitant viral infections,
- dermatologic disorders,
- patients on certain drugs, and also
- previously healthy subjects.

Interestingly, in the past, only a few patients were reported in whom an association of acquired haemophilia A with respiratory disorders such as chronic obstructive pulmonary disease was observed (9, 20). In approximately 50 to 60% of cases, autoantibodies against FVIII:C are detected in patients with serious or life-threatening haemorrhages who are lacking any relevant concomitant disease (5, 9, 14).

The incidence of acquired haemophilia A increases with age, and it is likely that this haemostatic disorder is underdiagnosed in the elderly (22). The age distribution of autoantibodies against FVIII:C is typically biphasic with (5, 7)

- a small peak in women between 20 to 40 years of age, due to inhibitors associated with pregnancy or the postpartum state,
- a major peak in patients aged 65 to 85 years.

In any case, acquired haemophilia A is associated with increased morbidity and mortality. In the past, fatal bleeding was high, ranging from 22% (9) to 31% (15) in several series related to age, persistence of inhibitor levels, and resistance to treatment (4, 5, 9, 15). The mortality rate has decreased in recent years and is currently at 9% (5).

We now report on the 10-year experience of our monocenter study conducted on 29 patients with regard to the overall outcome and their clinical features. In comparison to other reports (9, 12, 14), an interim analysis of our patients suggests a shift in underlying disorders associated with acquired haemophilia A. Thus, we observed an increase in the proportion of patients with respiratory disorders, specifically in chronic obstructive pulmonary disease (COPD).

**Patients, methods**

**Patients**

The study was conducted on 29 consecutive patients with acquired haemophilia A who were referred for diagnosis and treatment of the Düsseldorf Haemophilia Comprehensive Care Center (HCCC) between March 2001 and February 2010. The cohort of patients included 18 men (age range: 44–86 years) and 11 women (age range: 20–83 years). In only two of the 29 patients (7%), the diagnosis of acquired haemophilia A was made prior to admission to the Düsseldorf HCCC.

Despite prolonged APTT, surgery had been performed in five patients resulting in major postoperative haemorrhagic complications. According to the Declaration of Helsinki, informed consent was obtained from all patients participating in this single-center study.

**Laboratory methods**

For evaluation of haemostasis, a standardized staged protocol of aPTT, FVIII:C activity and concentration, mixing studies with patient and normal plasma, and quantification of inhibitor titers (Bethesda assay) was applied, using established procedures. Samples of whole blood were collected in vacuum tubes containing 3.8% (w/v) sodium citrate in a ratio of 1:9 (v/v) anticoagulant to blood. APTT and FVIII:C were determined on a Behring Coagulation System (BCS) by established coagulometric methods using Pathromtin SL or FVIII-deficient plasma (Siemens Health Care Diagnostics, Marburg, Germany, formerly Dade Behring), as described previously (8).

The FVIII:C reference plasma (Siemens Health Care Diagnostics) was calibrated against the WHO standard (10). Residual FVIII:C activity was measured photometrically using a two-stage chromogenic assay (Siemens Health Care Diagnostics, Newark, DE, USA). FVIII:Ag was determined by ELISA (Affinity Biologicals, Ancaster, ON, Canada) accordingly to the manufacture’s instructions. Mixing studies with patient and normal plasma were performed by conventional coagulometric techniques (8). For quantification of autoantibodies against FVIII, the Nijmegen modification of the Bethesda assay was used (13, 24). Inhibitor titers were expressed in Bethesda units (BU).

To exclude any other disorder than acquired haemophilia A, the haemostasis profile also included testing for the activity of factors II, V, VII, X (Thromborel S assay, Siemens Health Care Diagnostics), IX, XI, XII, and XIII (Berichrom assay, Siemens Health Care Diagnostics), screening of lupus anticoagulant, using a lupus sensitive APTT (Pathromtin SL, Siemens Health Care Diagnostics), the DVV test and the DVV confirmation test (American Diagnostica, Pfungstadt, Germany). In addition, evaluation of the von Willebrand profile was performed, including determinations of the ristocetin cofactor activity (Siemens Health Care Diagnostics) and plasma concentration of VWF (Instrumentation Laboratory, Milan, Italy).

**Diagnostic work-up**

A standardized staged protocol of clinical examinations and imaging procedures for any underlying disorder associated with acquired haemophilia A was used including a clinical pathology profiling, X-ray examination of the thorax, sonography of the abdomen, retroperitoneum and the thyroid gland, and various indications of computerized tomography of the thorax, abdomen, or pelvis.

**Study protocol**

For control of active bleeding, elimination or eradication of the inhibitor, and induc-
tion of immunotolerance to endogenous FVIII, we used a treatment algorithm, as depicted in Figure 1. In patients with acute bleeding symptoms, antihaemorrhagic therapy was initiated without any delay using FVIII bypassing agents (i.e., recombinant FVIIa, NovoSeven® and/or activated prothrombin complex concentrates (aPCC), FEIBA®). Immunosuppression (prednisolone alone or, sequentially, in combination with cyclophosphamide as first-line treatment; rituximab as second-line therapy if first-line immunosuppression failed) was started immediately following diagnosis. Details of the regimens will be reported elsewhere (19). Predefined clinical endpoints were control of bleeding, eradication of the inhibitor, complete or partial remission, relapse, or early death (≤30 days). In accord with others (5), complete remission required the following criteria:

- normalization of FVIII:C activity (>80%),
- no inhibitor detectable, and
- withdrawal of immunosuppressive therapy, or
- reduction to dosages of immunosuppressants administered prior to acquired haemophilia A.

For example, patients with a pre-existing autoimmune disorder required low-dose steroids that had to be continued, even when they had remitted from their acquired haemophilia.

Partial remission, as used in this study, was defined by increase of FVIII:C activity (>50% but <80%), decreased but still detectable inhibitor (irrespective of the exact titer), requirement of immunosuppression but no bleeding diathesis at all for more than 6 months. With regard to inhibitor titers, no cut-off value was set to define partial remission because antibody levels against FVIII are neither useful for decision making of treatment nor an indicator of outcome (5, 11). However, inhibitor levels over time may be a predictive indicator with regard to response to immunosuppressive therapy (11).

### Results

#### Presenting characteristics

Upon admission, only two of the 29 patients presented with minimal bleeds despite isolated prolongation of aPTT and subsequent identification of strongly reduced FVIII:C activity (<10%) with evidence of an inhibitor against FVIII:C. Of the other 27 patients, 15/29 (52%) had life-threatening bleedings with haemoglobin levels of less than 7.0 g/dl requiring transfusions of packed RBC, while 12/29 (41%) presented with non-vital extended ecchymoses and/or haemorrhages into muscles or soft tissues. Seven patients had gastrointestinal or urogenital bleeds. A typical cutaneous bleeding pattern of patients with acquired haemophilia A is depicted in Figure 2.

Among the 15 individuals with life-threatening bleeding complications was one patient with an extended retroperitoneal haematoma. Two other patients had developed cervical collar-like haemorrhages due to multiple unsuccessful attempts of puncturing the vena jugularis to get access for a central venous line. This manoeuvre had been undertaken prior to the patients’ transfer into our center. None of the patients presented with intracranial haemorrhage or developed this type of bleeding complication during the course. The distribution pattern and sites of bleeding in our patient population are shown in Figure 3.

### Underlying diagnosis

In 18 of the 29 patients (62%), an underlying disorder associated with acquired haemophilia A was identified. Seven of them had a pre-existing autoimmune disease (including three subjects with rheumatoid arthritis, two with autoimmune thyroiditis, and each one with multiple sclerosis or sarcoidosis). Nine patients suffered from respiratory disease, 8 had COPD, one asthma bronchiale. In one patient, a malignant melanoma was diagnosed; another one had a postpartum state. In 11 of 29 patients (38%), no underlying disorder could be detected. Thus, idiopathic acquired haemophilia was suggested. Figure 4 summarizes the data of the Düsseldorf Study in comparison to those from Heidelberg which were also evaluated in a single-center study.

### Overall outcome

Of the 29 patients in total, 22 individuals achieved complete remission (76%), three had a partial remission, one relapsed, and three died within 30 days. Among the cases...
of death, one patient suffered from acute myocardial infarction while still on anti-haemorrhagic treatment, one patient died of acute sepsis and subsequent multiple organ failure while on immunosuppression, one patient with pre-existing pulmonary sarcoidosis died of lung bleeding in association with active acquired haemophilia A. Details of individual patients with respect to their specific treatment and outcome have been published (23) or will be reported elsewhere (19).

Discussion

The interim analysis of this monocenter study conducted on a limited number of patients stresses several features of acquired haemophilia A.

1. A major characteristic of this rare haemostatic disorder is given by the fact that its bleeding pattern differs significantly from that of congenital haemophilia. Thus, most patients with autoantibodies against FVIII have haemorrhages into skin, muscles and soft tissues, or mucous membranes (including epistaxis, gastrointestinal or urogenital bleeds), retroperitoneal hematomas, or intracranial haemorrhages. By contrast, haemarthroses, a classic feature of congenital FVIII deficiency, are uncommon in acquired haemophilia (2, 7, 9). Moreover, haemorrhages are much more severe in acquired than congenital haemophilia. Although this is a general clinical experience, the reason for the different bleeding phenotype with regard to localisation and severity is poorly understood. This is also in contrast to drug-induced haemorrhages, for example in patients using antithrombotic drugs (17, 18).

2. Acquired haemophilia A appears to be more difficult to diagnose in general clinical practice than otherwise suggested by well-trained haemostasis consultants. Thus, those patients are seen in an array of clinical settings that are not usually equipped to tackle them (16). Among the individuals recruited for this study, only in two of the 29 patients (7%), the diagnosis of acquired haemophilia A had been made prior to admission to the Düsseldorf HCCC. Moreover, despite prolonged aPTT, five patients had undergone surgery, and in two other patients hazardous invasive manoeuvres had been performed, resulting in major postoperative or postprocedural haemorrhagic complications, respectively. These observations suggest that acquired haemophilia is underdiagnosed and also underestimated with regard to its life-threatening complications.

3. Even in specialized centers, appropriate treatment of high-risk patients with...
autoantibodies to FVIII and severe haemorrhagic complications remains challenging. This is due to the fact that, in the majority of cases, elderly patients are affected who have a high rate of comorbidity (6). Thus, anti-haemorrhagic treatment, any kind of immunosuppression and various procedures of inhibitor elimination regimens (i.e., extracorporeal circulation either for immunoadsorption or plasmapheresis) will require careful risk-benefit weighting in the individual patient. To date, no guidelines exist. However, recently published international recommendations on “how to treat” patients with acquired haemophilia are helpful (7, 11).

In accord with these recommendations, we have designed a treatment algorithm shown in Figure 1. This approach is based on a concise and straightforward diagnostic work-up with synopsis of clinical and laboratory findings. A mandatory element of this concept is the immediate interdisciplinary examination with imaging procedures including X-ray, sonography, and whenever required, computerized tomography. This program is essential to identify or exclude any underlying disorder associated with acquired haemophilia.

- provide a rational basis for careful risk-benefit assessment,
- allow appropriate decision making with regard to the kind and intensity of immunosuppression, and, when life-threatening bleeding persists,
- escalate treatment by application of inhibitor elimination regimens such as immunoadsorption and/or plasmapheresis.

In this study, immunosuppressive therapy was immediately initiated throughout, whenever possible. Using prednisolone alone or, sequentially, in combination with cyclophosphamide (either regimens as first-line treatment) and rituximab (as second-line immunosuppression) (Figure 1), 25 of the 29 patients (86%) recovered from acquired haemophilia A, 22 patients achieved complete (76%), and three had partial remission (10%). However, 15 of the 29 patients (52%), namely those with lifethreatening bleeds also required inhibitor elimination procedures by immunoadsorption (n = 11) and/or plasmapheresis (n = 6). Details will be discussed in another publication (19).

More recently, there has been an increasing tendency to administer rituximab primarily for eradication of FVIII inhibitors with durable responses (for review: 7, 11, 16). Several small series have provided promising results with complete remission rates of >80% in acquired haemophilia A, when this monoclonal antibody (against the pan B-cell antigen CD20) is used as first therapy (1, 21, 25), capable of inducing a rapid in vivo depletion of normal B lymphocytes (3). However, in these trials the follow-up was usually too small to draw definite conclusions. Currently, therapy with rituximab in association with other immunosuppressive agents as first-line treatment is discussed for patients with high-titer FVIII autoantibodies (7). In agreement with others (11, 16), we used rituximab in this single-center study only after complete failure of or inadequate response to the above immunosuppressive regimens. It should be stressed that rituximab, apart from its potential side effects, is not officially approved for this indication and therefore represents an off-label use in acquired haemophilia.

Another serious concern with respect to eradication of autoantibody inhibitors to FVIII is that immunosuppressive agents can cause severe side effects, particularly in elderly patients with significant co-morbidity. Sepsis resulting from or in association with immunosuppression in high-risk patients has been the most commonly reported adverse event in acquired haemophilia (5, 22). In the UK multicenter study* n = 29

<table>
<thead>
<tr>
<th>disorder</th>
<th>study, number of patients (%)</th>
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<tbody>
<tr>
<td>Düsseldorf Study*</td>
<td>n = 29</td>
</tr>
<tr>
<td>Heidelberg Study* Huth-Kühne</td>
<td>n = 42</td>
</tr>
<tr>
<td>UK Study§ Collins et al. [5]</td>
<td>n = 150§</td>
</tr>
<tr>
<td>Kessler &amp; Ludlam§ [14]</td>
<td>n = 65</td>
</tr>
<tr>
<td>Green &amp; Lechner§ [9]</td>
<td>n = 178##</td>
</tr>
<tr>
<td>none</td>
<td>11 (37.9)</td>
</tr>
<tr>
<td>autoimmune disease</td>
<td>7 (24.1)</td>
</tr>
<tr>
<td>rheumatoid arthritis</td>
<td>3 (10.3)</td>
</tr>
<tr>
<td>systemic lupus erythematosus</td>
<td>none</td>
</tr>
<tr>
<td>malignancy</td>
<td>1 (3.5)</td>
</tr>
<tr>
<td>dermatologic disorders</td>
<td>none</td>
</tr>
<tr>
<td>respiratory disease</td>
<td>9 (31.0)</td>
</tr>
<tr>
<td>asthma</td>
<td>1 (3.5)</td>
</tr>
<tr>
<td>COPD</td>
<td>8 (27.6)</td>
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<tr>
<td>pregnancy-related or post-partum</td>
<td>1 (3.5)</td>
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| Tab. 1 Underlying disorders in patients with acquired haemophilia A |

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<th>disorder</th>
<th>study, number of patients (%)</th>
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autoimmune disease 7 (24.1) autoimmune disease 3 (10.3) autoimmune disease 1 (3.5) autoimmune disease 9 (31.0) autoimmune disease 5 (3.3) autoimmune disease 1 (3.5) autoimmune disease 8 (27.6) autoimmune disease 6 (14.3) autoimmune disease 3 (2.0) autoimmune disease 7 (10.8) autoimmune disease 13 (7.3) autoimmune disease 3 (2.0)

The underlying disease was recorded in §150 of 172 or ##178 of 215 patients, respectively.
study, sepsis contributed to the death of 12 of the 167 patients (7%) who were retrospec-
tively analyzed for inhibitor eradica-
tion and survival following immunosup-
pression. In our monocenter trial, one early
death was due to septicemia. Another pa-
tient died of acute myocardial infarction
while still on haemotherapy with rFVIIa.
Thus, it cannot be ruled out that prothrom-
botic effects of antihaemorrhagic treat-
ment contributed to this fatal outcome.

Conclusion

As a result of the elaborate diagnostic work-
up that was performed throughout this
monocenter study, we were able to identify an
underlying disorder associated with acquired
haemophilia A in 18 of the 29 patients (62%)
(Fig. 4). This proportion is higher than that
of older and recent single- and multicenter
studies, ranging between 37 and 54% (Tab.
1). Thus, we conclude that comprehensive
clinical, laboratory and imaging examina-
tions being evaluated interdisciplinarily are
essential for complete diagnosis in patients
with acquired haemophilia.

With respect to underlying disorders,
another distinct feature of this study is the
high proportion (31%) of patients with re-
spiratory disease (Fig. 4; Tab. 1). In the
past, only a few studies reported on patients
with autoantibody inhibitors to FVIII and
concomitant pulmonary disease (9, 20).
For example, Shaffer et al. identified two
subjects with COPD in a small series of 9
patients (20). In the multicentric survey on
nonhaemophilic patients with inhibitors to
FVIII by Green and Lechner including 215
patients, only 7 of 178 patients had res-
spiratory disorders (3.9%), among them 5
individuals with asthma (9). By contrast,
the recent UK multicenter study did not
identify any patient with respiratory dis-
orders among 150 of 174 patients whose
underlying diagnosis was recorded (5).
Likewise, in the Heidelberg single-center
study by Huth-Kühne, none of the patients
suffered from pulmonary disease (12). In
comparison to these data, the proportion of
patients with COPD found in our study is
unusually high. By contrast, the rate of pa-
tients with autoimmune disorders (24% in
this study) is similar to that reported by
others (Tab. 1).

Although these “clusters” of auto-
immune and respiratory diseases may be
due to patient selection or could be biased
by small numbers, the high proportion of
patients with respiratory disease can be
indicative of a shift in underlying disorders
associated with acquired haemophilia. This
observation deserves special attention and
requires confirmation in larger studies.

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Conflict of interests

The authors state that they have no
conflict of interests.

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