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Von Willebrand disease

Walker-Warburg syndrome

orphanaesthesia

a project of the German Society
of Anaesthesiology and Intensive Care Medicine

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OrphanAnesthesia –
ein krankheitsübergreifendes Projekt des Wissenschaftlichen Arbeitskreises Kinderanästhesie der Deutschen Gesellschaft für Anästhesiologie und Intensivmedizin e.V.

Ziel des Projektes ist die Veröffentlichung von Handlungsempfehlungen zur anästhesiologischen Betreuung von Patienten mit seltenen Erkrankungen. Damit will Orphan Anesthesia einen wichtigen Beitrag zur Erhöhung der Patientensicherheit leisten.

Patienten mit seltenen Erkrankungen benötigen für verschiedene diagnostische oder therapeutische Prozeduren eine anästhesiologische Betreuung, die mit einem erhöhten Risiko für anästhesieassoziierte Komplikationen einhergehen. Weil diese Erkrankungen selten auftreten, können Anästhesisten damit keine Erfahrungen gesammelt haben, so dass für die Planung der Narkose die Einholung weiterer Information unerlässlich ist. Durch vorhandene spezifische Informationen kann die Inzidenz von mit der Narkose assoziierten Komplikationen gesenkt werden. Zur Verfügung stehendes Wissen schafft Sicherheit im Prozess der Patientenversorgung.

Die Handlungsempfehlungen von OrphanAnesthesia sind standardisiert und durchlaufen nach ihrer Erstellung einen Peer-Review-Prozess, an dem ein Anästhesist sowie ein weiterer Krankheitsexperte (z.B. Pädiater oder Neurologe) beteiligt sind. Das Projekt ist international ausgerichtet, so dass die Handlungsempfehlungen grundsätzlich in englischer Sprache veröffentlicht werden.

Ab Heft 5/2014 werden im monatlichen Rhythmus je zwei Handlungsempfehlungen als Supplement der A&I unter www.ai-online.info veröffentlicht. Als Bestandteil der A&I sind die Handlungsempfehlungen damit auch zitierfähig. Sonderdrucke können gegen Entgelt bestellt werden.

Bisher in A&I publizierte Handlungsempfehlungen finden Sie unter:

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OrphanAnesthesia –
a common project of the Scientific Working Group of Paediatric Anaesthesia of the German Society of Anaesthesiology and Intensive Care Medicine

The target of OrphanAnesthesia is the publication of anaesthesia recommendations for patients suffering from rare diseases in order to improve patients' safety. When it comes to the management of patients with rare diseases, there are only sparse evidence-based facts and even far less knowledge in the anaesthetic outcome. OrphanAnesthesia would like to merge this knowledge based on scientific publications and proven experience of specialists making it available for physicians worldwide free of charge.

All OrphanAnesthesia recommendations are standardized and need to pass a peer review process. They are being reviewed by at least one anaesthesiologist and another disease expert (e.g. paediatrician or neurologist) involved in the treatment of this group of patients.

The project OrphanAnesthesia is internationally oriented. Thus all recommendations will be published in English.

Starting with issue 5/2014, we'll publish the OrphanAnesthesia recommenations as a monthly supplement of A&I (Anästhesiologie & Intensivmedizin). Thus they can be accessed and downloaded via www.ai-online.info. As being part of the journal, the recommendations will be quotable. Reprints can be ordered for payment.

A survey of until now in A&I published guidelines can be found on:

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Projektleitung
Prof. Dr. Tino Münster, MHBA
Chefarzt
Klinik für Anästhesie und operative Intensivmedizin
Krankenhaus Barmherzige Brüder Regensburg
Prüfeninger Straße 86
93049 Regensburg,
Deutschland
Tel.: 0941 369-2350
E-Mail: Tino.Muenster@barmherzige-regensburg.de

DGAI
Deutsche Gesellschaft für Anästhesiologie & Intensivmedizin
www.dgai.de

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ANÄSTHESIOLOGIE & INTENSIVMEDIZIN
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orphananesthesia

Anaesthesia recommendations for

Von Willebrand disease

Disease name: Von Willebrand disease

ICD 10: D68.0

Synonyms: Inherited bleeding disorder

Von Willebrand disease (VWD) is the most common inherited bleeding disorder. Most cases are transmitted as an autosomal dominant trait, although with variable penetrance.

There are three major types of VWD disease. Type 1, the most frequent form, is characterised by a partial quantitative deficiency in von Willebrand factor (VWF). Type 2 is a qualitative deficiency, and type 3 is a virtually complete deficiency. Type 2 VWD is divided into four subtypes. Type 2A includes variants with decreased platelet adhesion caused by a selective deficiency in high-molecular weight VWF multimers (HMWM). Type 2B includes qualitative VWF variants with an increased affinity to platelet glycoprotein Ib. Type 2M includes variants with decreased platelet adhesion, but without HMWM deficiency, and type 2N includes variants with markedly decreased affinity for factor VIII. This categorisation correlates with therapeutic requirements.

Medicine in progress

Perhaps new knowledge

Every patient is unique

Perhaps the diagnosis is wrong

Find more information on the disease, its centres of reference and patient organisations on Orphanet: www.orpha.net

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Disease summary

VWF is a plasma glycoprotein produced in megakariocytes and endothelial cells. It plays an important role in primary haemostasis through the mediation of initial platelet adhesion to sites of vascular injury. It also binds and stabilises factor VIII (FVIII) in the blood.

VWD diagnosis, especially type 1, may be difficult. In mild cases, VWF levels may overlap with those of normal subjects. The clinical manifestations of the disease may vary from minimal to severe. However, the bleeding risk generally parallels VWF levels. Given that a mild decrease of VWF levels is relatively common, the prevalence of the disease varies among studies and can be as high as 1% in the general population. As a consequence, only a fraction of patients come to medical attention because of bleeding symptoms. A definite diagnosis of VWD type 1 is performed when VWF:Ag is <30 IU/dL, in association with bleeding symptoms. Persons with VWF:Ag levels of 30–50 IU/dL are considered to have a low VWF level, but not a VWD. They may also be at risk of bleeding. During the pre-operative evaluation of those patients, the presence of bleeding symptoms should always outweigh the VWF levels in assessing the bleeding risk. Among the signs that should draw the attention of the practitioner, the most common are recurrent and prolonged nosebleeds, bleeding from the gums, increased menstrual blood losses, excessive bleeding from a cut or following a tooth extraction, easy bruising, and family history.

Typical surgery

These patients can be addressed for every type of surgical procedure, but should be managed in centres where a multidisciplinary team and daily laboratory testing of the factors involved are available. Patients managed within specialised haemostasis and thrombosis hospital centres have a favourable prognosis, even for severe forms of the disease.

Type of anaesthesia

General anaesthesia is often preferred in these patients. It is noteworthy that regional anaesthesia must be performed with caution, particularly when spinal and epimedullar anaesthetic procedures are planned. In this case, no formal recommendations exist and contraindications are relative. Should a neuraxial technique be used, neurological postoperative surveillance is mandatory due to the increased risk of developing an epi-medullar haematoma and compressing neurological structures. In case of neurological symptoms, the diagnosis is confirmed by CT or MR imaging. Radiographies of the spine are useless.

Each patient should be managed individually on a case-by-case basis according to his/ her sub-type of VWD, severity, and the relative amount of circulating VWF antigen (VWF:Ag), VWF ristocetin cofactor (VWF:RCo), and FVIII pro-coagulant activity (FVIII:C) at the time of the procedure.

Necessary additional diagnostic procedures (preoperative)

A simple, single laboratory test to screen for VWD is not available. In addition, the results of initial coagulation tests, such as prothrombin time (PT) and activated partial thromboplastin time (aPTT) may be normal. The aPTT reagents are sensitive to FVIII:C plasma levels lower

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than 30 IU/dL, whereas the test may turn out normal when the FVIII level is greater than 40 IU/dL.

Routine coagulation tests should be performed in case of clinical suspicion which arises during the preoperative interview. They vary among surgical teams. They may consist of platelet count, PT, aPTT, fibrinogen concentration, platelet function analysis (PFA-100®, Siemens Healthcare), and eventually FVIII:C, VWF:Ag, VWF:RCo. In type 1, there is an equivalent reduction of VWF:Ag and VWF:RCo. An abnormal VWF:RCo/VWF:Ag ratio (< 0.6) is a simple way to suspect type 2 VWD.

The PFA-100® test has been demonstrated to produce abnormal values in the majority of VWD patients when VWF is significantly decreased, but values are normal in patients with type 2N. However, the usefulness of PFA-100® in screening populations for VWD has not been established.

Other laboratory tests to be performed are a count of blood cells (CBC), blood group, C-reactive protein (CRP), and ferritin (see below).

A Watson-Williams questionnaire is recommended during the preoperative evaluation. For patients with a family history of strong bleeding, with current symptoms, or a history of increased muco-cutaneous bleeding, and those with a previous VWD diagnosis without laboratory documentation, specific VWD assays should be considered at the first visit.

If the initial VWD assay is positive, patients should be referred to a haemostasis specialist in order to further investigate their VWD sub-type and its responsiveness to desmopressin (DDAVP). Indeed, a test dose of DDAVP is recommended in VWD patients to establish the pattern of biological response and predict clinical efficacy. The response in an individual adult patient is constant over time. This desmopressin trial should be performed in non-bleeding patients. The haemostasis specialist will also establish a multidisciplinary management plan in preparation to surgery or an invasive procedure.

It is noteworthy that several conditions such as systemic inflammation (evidenced by elevated CRP and ferritin), pregnancies, oestrogen or oral contraceptives, as well as stress (surgery, exercise, anxiety, crying frightened child, etc.) can increase the plasma level of VWF and mask lower baseline values. Of note is also that mean VWF levels are 25% lower in persons with type-0 blood group. VWF is also low in patients with hypothyroidism.

Particular preparation for airway management

None but traumatic orotracheal intubation (OTI) should be avoided. Special attention should be paid to patients with increased risk of difficult intubation such as in the obstetric and paediatric population. In case of difficult intubation, the use of a fibrescope or video-laryngoscope may reduce the risk of bleeding and mucosal lesions.

Particular preparation for transfusion or administration of blood products

It is recommended that candidates for replacement therapy with VWF/FVIII concentrate benefit from a vaccination against hepatitis A and B.

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Particular preparation for anticoagulation

Patients with VWD should be advised to avoid nonsteroidal antiinflammatory drugs (NSAIDs), acetylsalycilic acid, and any type of platelet-inhibiting medications.

Low-dose heparin prophylaxis should be considered in the perioperative period of surgeries with a high thrombotic risk, especially when a replacement treatment is administered.

Particular precautions for positioning, transport or mobilisation

Avoiding any trauma during positioning, transport and mobilisation is the rule.

Probable interaction between anaesthetic agents and patient's long term medication

None reported.

Anaesthesiologic procedure

VWD therapies follow three general strategies. The first aims at increasing the plasma concentration of VWF by an endogenous release by desmopressin. The second strategy uses agents that improve haemostasis (tranexamic acid, aminocaproic acid), without modifying the plasma levels of VWF. The third approach aims at replacing VWF by human-plasma-derived, virus-inactivated concentrates. The range of available products varies from one country to another. The following list provides examples of such products and is not exhaustive: Haemate P®(CSL Behring), Wilate®(Octapharma), Alphanate®(Grifols), Fanhdi®(Grifols), Biostate®(CSL Behring), Dried factor VIII fraction type 8Y®(Bio Products Laboratory), Immunate®(Baxter), Wilfactin®(C.A.F – D.C.F).

The appropriateness of the therapeutic choice depends on VWD severity and type, severity of the haemostatic challenge, and the nature of the actual or potential bleeding.

For minor surgery, prophylaxis should achieve VWF:RCo and FVIII:C levels of ≥ 50 IU/dL on the day of surgery and during the first postoperative day, and > 30 IU/dL during 2 to 5 days thereafter, or until scab falls. For major surgery, such as cardiac or neurosurgery, the levels of VWF:RCo and FVIII:C should be around 100 IU/dL on the day of surgery and on the first postoperative day, and should be maintained at ≥ 50 IU/dL for 7 to 14 days or until healing is complete.

Desmopressin:

Desmopressin stimulates VWF release by means of its agonist effect on vasopressin V2 receptors. FVIII levels also increase acutely following its administration. When administered intravenously in healthy patients, it increases plasma VWF and FVIII from two to fivefold over baseline levels. Children younger than 2 years have a lower response rate than older children. The standard dose is 0.3 µg kg^{-1}. This dose must be diluted in 50 to 100mL isotonic saline and infused intravenously over 30 minutes. In such case the peak effect will occur within 30 to 90 minutes. A concentrated formulation for subcutaneous administration is also available. Desmopressin may eventually be repeated every 12 hours but its response diminishes with repeated administration (tachyphylaxis). Desmopressin provokes a release

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of VWF from internal cell storage. Hence, once empty, no more VWF can be released from them. In addition to tachyphylaxis, hyponatraemia may complicate repeated administration. Ionic monitoring, fluid restriction, and isotonic infusions are recommended, particularly in children. Adult patients and particularly elderly patients should be evaluated for potential cardiovascular diseases. Indeed, a precipitation of myocardial infarction by desmopressin therapy has been reported, although rarely.

Desmopressin is usually effective in type 1 VWD. Type 2A patients rarely respond relevantly. Type 2B patients were previously considered as a contraindication to desmopressin. The reason was a frequent fall in platelet count after desmopressin stimulation. However, thrombocytopenia is usually transient and usually not associated with bleeding or thrombosis. Hence, type 2B is a relative contraindication. In type 2M, the efficacy of desmopressin is variable. In type 2N, desmopressin raises VWF, but very shortly. Patients with type 3 VWD do not respond to desmopressin at all.

Antifibrinolytic agents:

Currently, tranexamic acid (TXA) is the most widely used antifibrinolytic agent. The drug inhibits the conversion of plasminogen into plasmin, thereby stabilising previously formed clots. TXA can be used orally or intravenously. The dose and administration modes vary among teams. Intravenously, the bolus dose of TXA is 10-15mg kg^{-1} repeated every 8-12 hours or followed by a maintenance infusion of 10 mg kg^{-1} h^{-1}. If used as a wash-mouth for oral surgery, the frequency of administration can be increased. TXA is contraindicated for the management of renal or upper urinary tract bleeding because of the risk of ureteral clots and subsequent hydronephrosis.

Replacement therapy:

Replacement therapy aims at correcting VWF deficiency, allowing for platelet adhesion and aggregation, and increasing potentially low FVIII:C level. All plasma-derived concentrates contain both purified VWF and FVIII, except for one containing VWF only (see below). The main difference between products is the VWF:RCo/FVIII:C ratio. For example, the ratios of Haemate P®, Immunate®, Alphanate®, Fanhdi®, Biostate®, Dried factor VIII fraction type 8Y®, and Wilate® are 2.4/1, 0.5/1, 1.2/1, 1.15/1, 2/1, 3/1 and 1/1, respectively. It is noteworthy that the 1.2/1 ratio of Alphanate® is highly variable from one lot to another.

All these concentrates may be considered as bioequivalent in terms of their VWF pharmacokinetic properties. The Wilate® 1:1 VWF/FVIII ratio should in theory facilitate dosing and laboratory monitoring of VWF. However, it can also make FVIII increase to too high levels, particularly when its baseline concentration is only mildly reduced. Very high levels of FVIII increase the risk of thromboembolic events. All plasma-derived concentrates should be used with caution in patients with increased thrombotic risks, as there have been some reports of venous thromboembolism associated with high levels of FVIII. The risk is even higher when the replacement therapy is combined with an antifibrinolytic therapy.

Wilfactin® (C.A.F – D.C.F) is the only product that contains VWF uniquely. It is therefore not suitable for the immediate correction of low FVIII:C levels to haemostatic levels. Wilfactin® can be useful when the patient has normal or mildly low FVIII levels. When used for elective surgery, the first dose should be given 12 to 24 hours prior to surgery in order to provide adequate haemostasis, as there is a secondary rise of endogenous FVIII due to the stabilising effect of infused VWF. Switching to Wilfactin® should also be considered when combined VWF/FVIII therapy causes FVIII to assume too high levels, thereby increasing thromboembolic risks.

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+Adverse reactions to replacement therapy are rare, but may be severe and include allergic and anaphylactic symptoms, urticaria, chest tightness, rash, pruritus, and oedema. Severe allergic reactions may reveal the onset of an inhibitor against VWF, rarely and exclusively observed in some type 3 VWD patients. The dose of VWF concentrate should always follow the licensed product recommended dosage. Doses are usually given in labelled VWF:RCo units. One IU kKg^{-1} of VWF:RCo is considered to increase plasma VWF:RCo by approximatively 2%. The loading dose can be calculated as = (Δ×bw)/IVR, where Δ is the targeted VWF:RCo increase ($IU.dL^{-1}$) to achieve the desired plasma level, bw is the body weight in kilograms, and IVR is the half-life of incremental in-vivo recovery (IVR). VWF concentrate administration is usually repeated every 24 hours postoperatively. Maintenance doses should be adapted to the daily measured levels of FVIII:C and VWF:RCo. Monitoring of VWF:RCo and FVIII:C is also used to avoid the risk of perioperative thrombosis. VWF:RCo and FVIII:C levels should not exceed 150-200 IU/dL.

In an emergency situation, when the baseline level is unknown, the initial bolus dose is 50 IU kg^{-1}.

Particular or additional monitoring

Monitoring modalities are related to the type of surgery, and the risk of bleeding. Secure venous access is mandatory, but the necessity of an arterial catheter should be discussed on a case-by-case basis. Iterative arterial blood sampling through direct needle arterial puncture should be avoided.

Possible complications

The outbreak of an inhibitor against VWF or FVIII is one of the most severe encountered complications during the treatment of type 3 VWD patients.

Thromboembolic events due to the increase in FVIII can occur, as discussed above.

The risk of viral contamination following the administration of factor concentrate is very low, but not zero.

Postoperative care

The goal is to maintain normal FVIII:C and VWF:RCo levels as long as the haemostatic challenge persists. This period ranges between 1 to 5 days for minor surgery and up to 14 days for major surgery such as neurosurgery. Special care should be used for tonsillectomy, as scab falls with inherent risk of bleeding after 6–7 postoperative days. As mentioned above, factor levels should be monitored daily while replacement therapy is in progress and dosing should also be adapted to the obtained results. This management often results in prolonged hospitalisation times. Patients still require a close follow-up after being released from the hospital. Neurological evaluation after neuraxial blocks is mandatory.

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Information about emergency-like situations/ Differential diagnostics

In case of an uncontrolled haemorrhage despite adequate VWF:RCo/FVIII:C levels, and after the exclusion of an anatomic aetiology, platelet transfusion should be considered in addition to the administration of a supplementary FVIII-VWF concentrate and/or desmopressin in responsive patients. These measures will most often stop the bleeding. In case of an uncontrolled haemorrhage and inadequate VWF:RCo/FVIII:C levels despite proper administration, the rare possibility of an inhibitor should be kept in mind, especially in case of type 3 VWD. As such an event is particularly rare, a recommendable therapy has not been defined yet. Possible therapeutic approaches include the application of recombinant factor VIII or by-passing agents such as recombinant factor VIIa (rFVIIa).

Ambulatory anaesthesia

Only a patient with a mild type VWD and scheduled for a low bleeding risk surgery can safely benefit from ambulatory anaesthesia.

Obstetrical anaesthesia

As a reminder: each patient is unique. Management should be discussed on a case-by-case basis.

Non-anaesthetic considerations:

- Genetic counselling is desirable, optimally before conception, particularly to those at risk of having a child with type 3 VWD.
- Even though there appears to be a higher incidence of vaginal bleeding in pregnant women with VWD during the first trimester, there is no increase in the miscarriage rate.
- An inherited bleeding disorder in the mother or foetus is by itself not an indication for caesarean section delivery. The mode of delivery should be determined by obstetrical considerations.
- Neonates at risk of significant VWF decrease are at risk of head bleedings (scalp haematoma and intracerebral haemorrhage) during labour and delivery. Hence, the use of invasive foetal heart-rate monitoring techniques and instrumental deliveries should be avoided.
- Pregnancy in women with VWD should be managed by an multidisciplinary team of experts, including an obstetrician, a specialist in haemostasis, and an anaesthesiologist. It should be conducted in centres where resources for laboratory testing and clotting factor treatments are readily available.

Normal pregnancy and childbirth are associated with significant haemostatic changes that create a procoagulant state. This occurs through an increase in the majority of clotting factors, including FVIII and VWF.

Factor levels, including FVIII:C, VWF:Ag, and VWF:RCo, should be measured at presentation and at least once during the third trimester, as well as before any invasive procedure.

Changes in VWF during pregnancy vary according to VWD type. In type 1 VWD, FVIII:C, VWF:Ag, and VWF activity usually increase progressively. The most significant increase

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occurs during the third trimester and most women achieve normal ranges of VWF by the third trimester. In type 2 VWD, FVIII:C and VWF:Ag levels often increase, but most studies show minimal or no increase in VWF activity at all, as well as a persistently abnormal pattern of multimers, reflecting the increased production of abnormal VWF. Women with type 3 VWD show little or no increase in FVIII and VWF plasma levels.

As a consequence, neuraxial anaesthesia is often possible in women suffering from type 1 VWD. However, VWF and FVIII must be > 50 IU/dL, and this must be documented by laboratory tests during the third trimester. If an epidural catheter is used, preferably a round-tip catheter, the epidural space should be well dilated before its introduction. Even with these recommendations, there is a risk of neuraxial hematoma.
Neuraxial anaesthesia is usually not recommended in type 2 and 3 VWD. Exceptions are possible when the factor levels are above 50 IU/dL following a prophylactic treatment.
It is recommended that normal levels shall be maintained for the duration of catheter placement, and for 12 to 24 hours after catheter removal, as the levels of FVIII and VWF decrease rapidly after uterine emptying. In any case, the neuraxial blocks must be carried out by an experienced anaesthesiologist and repeated attempts to puncture should be avoided.

Prophylactic treatment should be given when factor levels are below 50 IU/dL in order to cover invasive procedures and delivery. Desmopressin can and has been safely used during pregnancy, particularly during the first trimester of pregnancy to cover invasive procedures such as villocentesis and amniocentesis, but it should be used cautiously during gestation. Repeated administrations or use in preeclamptic patients should be avoided. Close monitoring for water retention must be the rule. Tranexamic acid can also be used for the prevention or control of postpartum haemorrhage (PPH). Due to the lack of studies investigating its use during pregnancy, no guidelines exist. However, it has been used successfully and without eliciting apparent adverse maternal or foetal effects according to a few case reports found in the literature. Replacement therapies follow the same scheme as described above. In women who require clotting factors replacement, FVIII:C and VWF:Ag levels should be monitored daily and maintained above 50 IU/dL for at least 3 to 5 days, and up to 7 days in case of caesarean section.

Factor levels that may have normalised during pregnancy tend to return to baseline within 7 to 21 days after delivery.

Women with VWD have a significantly higher risk of both primary and secondary PPH. Women with early PPH associated with low factor levels should be managed using factor replacement therapy or with desmopressin for those who are responsive. Desmopressin has been detected in the milk of lactating women. In breastfeeding mothers, factor replacement therapy should therefore be preferred. Tranexamic acid should be considered to prevent or control secondary postpartum haemorrhages. This medication is safe in breastfeeding mothers.

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This recommendation was prepared by:

Authors

Vincent Bonhomme, Anaesthesiologist, CHR Citadelle, Liege, Belgium
vincent.bonhomme@chu.ulg.ac.be

Aline Defresne, Anaesthesiologist, CHR Citadelle, Liege, Belgium
alinedefresne@gmail.com

Isablle Maquoi, Anaesthesiologist, CHR Citadelle, Liege, Belgium

Jean-Marc Minon, Hematologist, CHR Citadelle, Liege, Belgium

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Peer revision 1

Dario Galante, Anaesthesiologist, University Hospital Ospedali Riuniti of Foggia, Italy
dario.galante@tin.it

Peer revision 2

Giancarlo Castaman, Hematologist, San Bortolo Hospital, Vincenza, Italy
castaman@hemato.ven.it

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E-Mail: anaesth.intensivmed@dgai-ev.de

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Pia Engelhardt
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Roritzerstraße 27, 90419 Nürnberg
Tel.: 0171 9432534 | Fax: 0911 3938195
E-Mail: jdistler@bda-ev.de

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ADDRESS

German Society of Anaesthesiology and
Intensive Care Medicine
Ursula Homberg
Roritzerstrasse 27 | 90419 Nuremberg | Germany
Tel.: +49-911-9337828 | Fax: +49-911-3938195
Email: uhomberg@orphananesthesia.eu