Haemophilia (2004), **10,** 218–231 DOI: 10.1111/j.1365-2516.2004.00886.x

Management of von Willebrand disease: a guideline from the UK Haemophilia Centre Doctors' Organization

K. J. PASI,* P. W. COLLINS,† D. M. KEELING,‡ S. A. BROWN,§ A. M. CUMMING,¶ G. C. DOLAN,** C. R. M. HAY,¶ F. G. H. HILL,†† M. LAFFAN‡‡ and I. R. PEAKE§§

**Department of Haematology, Barts and the London, Queen Mary's School of Medicine and Dentistry, London; †Arthur Bloom Haemophilia Centre, University Hospital Wales, Cardiff, Wales; ‡Oxford Haemophilia Centre, Churchill Hospital, Oxford; §Department of Haematology, Royal Free Hospital, London; ¶University Department of Haematology, Manchester Royal Infirmary, Manchester; **Department of Haematology, Queen's Medical Centre, Nottingham; ††Department of Haematology, The Children's Hospital, Birmingham; ‡‡Department of Haematology, Imperial College, Hammersmith Hospital, London; and §§Division of Genomic Medicine, University of Sheffield, Sheffield, UK*

Summary. von Willebrand disease (VWD) is the commonest inherited bleeding disorder. The aim of therapy for VWD is to correct the two defects of haemostasis in this disorder, impaired primary haemostasis because of defective platelet adhesion and aggregation and impaired coagulation as a result of low levels of factor VIII. The objective of this guideline is to inform individuals making choices about the treatment and management of VWD including the use of therapeutic products. This is the second edition of this UK Haemophilia Centre Doctors' Organization (UKHCDO) guideline and supersedes the previous edition which was published in 1994.

Keywords: blood products, 1-deamino-8-D-arginine vasopressin, guideline, inherited bleeding disorder, treatment, von Willebrand disease

Introduction

von Willebrand disease (VWD) is a congenital bleeding disorder resulting from a quantitative or qualitative deficiency of von Willebrand factor (VWF), a plasma glycoprotein with essential platelet-dependent functions in primary haemostasis and a carrier for factor VIII (FVIII) in the circulation. VWF circulates as a series of high-molecular weight (HMW) multimers, the larger multimers being essential for normal platelet-dependent VWF function under the high shear stress conditions present in the microvasculature. VWD is considered to be the commonest of the inherited bleeding disorders, usually presenting as a mild to moderate disorder typically with easy bruising or bleeding from mucosal surfaces. The current classification of VWD was introduced in 1994 [1] and is summarized as follows: type 1 VWD – a mild to moderate bleeding disorder resulting from a partial quantitative deficiency of VWF; type 2A VWD – a qualitative defect of VWF associated with the absence of HMW VWF multimers; type 2B VWD – a qualitative VWF defect characterized by increased binding to platelets, usually associated with the loss of HMW VWF multimers and often mild thrombocytopenia, type 2M VWD – a qualitative defect of VWF associated with defective interactions between VWF and platelets but not because of the loss of HMW VWF multimers; type 2N VWD – a qualitative variant resulting from defective binding of VWF to FVIII with resultant low levels of FVIII; type 3 VWD – a severe bleeding disorder resulting from an almost complete lack of VWF and consequently markedly reduced levels of FVIII.

Correspondence: Prof K. J. Pasi, Chairman of the UKHCDO von Willebrand Disease Working Party, Department of Haematology, Barts and The London, Queen Mary's School of Medicine and Dentistry, Turner Street, London E1 2AD, UK.
Tel.: +44 20 7377 7000 (x) 3152; fax: +44 709 222 7649;
e-mail: k.j.pasi@qmul.ac.uk.

Accepted after revision 14 January 2004

Aims of the guideline

The aim of the guideline is to provide contemporary advice on a rational approach to the management of VWD. Target users of the guideline include clinical staff involved in the care of patients and families

with VWD. Users of the guideline should be aware that individual professional judgement is not suspended on the basis of advice contained herein. This guideline will be reviewed annually by the UK Haemophilia Centre Doctors' Organization (UKHCDO) and updated when required.

Methods

The UKHCDO produced a previous guideline on the treatment and management of VWD in 1994 [2]. The guideline has been revised, updated and substantially rewritten in an attempt to define best current practice on the basis of evidence available in the literature.

This document has been produced by the UKHCDO VWD Working Party. The guideline writing group included UK-based medical and scientific experts in the diagnosis and treatment of inherited bleeding disorders, including VWD. Relevant scientific papers were identified by systematic review from Medline using the index terms VWF, VWD, FVIII, treatment and management. Further publications were obtained from the references cited and from reviews known to the members of the working party. Reports in the literature were used to establish the evidence upon which recommendations have been made. Recommendations are based on reports with the highest level of evidence available and the graded recommendations presented in these guidelines are in accordance with the US Agency for Health Care Policy and Research ([74]; see Appendix). It has been clear in the production of this guideline that there are a number of areas where only a consensus, rather than evidence-based, recommendation can be given.

Drafts were circulated to the Advisory Committee of the UKHCDO for consultation and editorial comment.

Therapeutic recommendations

In deciding upon treatment in VWD it is important to consider the following:

1 the nature of the bleeding episode;
2 the FVIII and VWF levels and the VWD subtype;
3 the patient's previous bleeding history and response to treatment;
4 the FVIII and VWF response to 1-deamino-8-D-arginine vasopressin or desmopressin (DDAVP) if previously given;
5 presence of an inhibitor;
6 potential risks of treatment.

The following guidelines for the treatment and management of VWD are presented in four major sections: pharmacological agents, blood products, treatment of specific problems and management of surgery.

Pharmacological agents

DDAVP

Mode of action, dosage and administration DDAVP, a synthetic vasopressin analogue, increases endogenous FVIII and VWF. DDAVP causes VWF to be released from endothelial stores. The mechanism for the rise in FVIII was thought to be due to its consequent stabilization in plasma [3]. However, its use in type 2N VWD has indicated that DDAVP must also release FVIII from a storage pool [4]. It is usually given by slow i.v. infusion of 0.3 μg kg^{-1} over 20 min. Typically the 4 μg mL^{-1} solution is made up in 50–100 mL of normal saline for infusion. A more concentrated solution (15 μg mL^{-1}) is available for s.c. use although it does not have a product licence in the UK. The s.c. dose of 0.3 μg kg^{-1} has a comparable effect with the same i.v. dose [5]. DDAVP can also be given as a nasal spray (150 μg per single spray), using a standard dose of 300 μg in an adult and 150 μg in a child – at this dose its effect approximates that of 0.2 μg kg^{-1} given i.v. [6]. This method is simple for the patient to administer at home [7]. Intranasal DDAVP is available in a special concentrated preparation, but at present this lacks the UK product licence. Adverse events may be more common with this preparation, although they are often mild [8].

Factor VIII:C and VWF levels increase to two to five times baseline with a peak at 60 min after the completion of i.v. infusion of DDAVP (90–120 min after s.c. and intranasal application). When monitoring responses, ideally a further sample should be obtained at 3–6 h to ensure that there is not a rapid fall off in levels. Further doses can be administered at 12 h intervals although the response should be monitored, as there may be a diminished response to successive doses in some patients.

Use in VWD DDAVP is a very valuable drug as it can often be used instead of blood products. When one has to choose between the two, unless otherwise contraindicated, if DDAVP is likely to be effective it will usually be potentially safer from blood-borne virus transmission and so is the treatment of choice. It is often effective in type 1 disease where increasing VWF levels two- to fivefold is sufficient for haemostasis. It is of no therapeutic use in type 3 VWD. In types 2A and 2M VWD, DDAVP increases the levels

of the abnormal VWF and has a variable clinical effect. These patients should have a trial of DDAVP to see if it is effective in their individual case. Responses are usually consistent so that patients can be labelled as responsive or not.

The use of DDAVP in type 2B VWD is controversial. It has been said to be contraindicated as the release of the abnormal VWF may induce platelet aggregation and thrombocytopenia [9]. However, it has been argued that the thrombocytopenia may be an *in vitro* artefact and that DDAVP is safe and may be clinically effective in type 2B disease [10–15]. Although DDAVP may be useful in selected clinical circumstances, data on the value of DDAVP in treatment of bleeding episodes in type 2B VWD is still scanty [16].

In a study of the use of DDAVP in type 2N VWD a median sevenfold increase in FVIII:C was observed [4] although because of the abnormal FVIII-binding there was a much reduced half-life (3 h in this study).

Adverse effects and contraindications Hypotension and facial flushing are not uncommon and may necessitate an i.v. infusion being slowed. Care with peri- and postoperative i.v. fluids should always be taken after the use of DDAVP to prevent fluid overload and consequent hyponatraemia, especially when repeated doses are used. During repeated administration the patient should be weighed regularly and serum electrolytes measured.

DDAVP should be avoided in patients with heart failure or other conditions being treated with diuretic agents. The data sheet gives unstable angina as a contraindication but after anecdotal reports of myocardial infarction [17–19] and cerebral infarction [20] it is best avoided in all patients with known atherosclerosis.

DDAVP is not contraindicated in uncomplicated pregnancy although like all drugs it should be used with caution. No teratogenic effect has been observed in animals and its prolonged use (at lower dosage) in diabetes insipidus has shown no adverse effects for mother or fetus [21]. DDAVP has a 1000-fold greater affinity for vasopressin type 2 (V2) receptors over the type 1 (V1) receptors and so has very little oxytocic effect. It would be prudent to avoid prolonged administration in pregnancy and to monitor closely for water retention (the fetus will of course have the same plasma sodium as the mother).

Some clinicians prefer not to use DDAVP in patients who are <2 years old because of the risk of hyponatraemia and seizures, which are increased in infants and young children [22,23]. If DDAVP is used in this age group, it should be used with caution and close surveillance, fluid restriction, avoidance of hyponatraemic solutions, and monitoring of serum electrolytes and urine output for at least 24 h after administration.

Recommendations

1 Due to the potential risks of infection blood products should be avoided if possible to treat VWD (grade C, level IV). DDAVP should be used in preference.
2 In type 1 VWD patients with baseline VWF levels >10 IU dL^{-1} DDAVP will often be an effective treatment (grade B, level III). If the patient has not had a trial of DDAVP, FVIII:C and VWF levels must be monitored during the first treatment to ensure an adequate response is obtained (grade C, level IV). Clearly the definition of an adequate response will depend, in part, upon the indication for treatment.
3 Patients with types 2A and 2M VWD should have a trial of DDAVP (grade C, level IV).
4 DDAVP can be used in type 2N VWD but the short half-life of the FVIII response should be taken into account (grade B, level III).
5 It is the opinion of many clinicians that DDAVP is contraindicated in patients with type 2B VWD. However, published data suggest it is reasonable to consider a trial of DDAVP (grade B, level III).
6 DDAVP is relatively contraindicated in children <2 years old. If after careful consideration it is to be used in this age group then fluid restriction, avoidance of hyponatraemic solutions, and close monitoring of serum electrolytes and urine output for at least 24 h after administration is warranted (grade B, level III).
7 Adults should be warned to limit fluid intake to 1 L in the 24 h after DDAVP (grade C, level IV).
8 DDAVP should be avoided in those with known atherosclerosis (grade C, level IV).

Tranexamic acid

Mode of action, dosage and administration Tranexamic acid is an antifibrinolytic agent. It binds to the lysine-binding sites of plasminogen thus inhibiting the binding of plasminogen to fibrin. In elective procedures it is therefore likely to be more effective if given beforehand so that it is circulating when fibrin is formed. It can be given orally (15–25 mg kg^{-1} tds) or i.v. (10 mg kg^{-1} tds). Alternatively it can be given as a mouthwash (10 mL of a 5% w/v solution four times a day). If the mouthwash is swallowed this will

provide 500 mg qds orally. The plasma half-life of tranexamic acid is 2 h.

Use in VWD Tranexamic acid can be used alone in the management of epistaxis and menorrhagia or in combination with DDAVP- or VWF-containing concentrates to cover dental extractions and surgery.

Adverse effects and contraindications Nausea, vomiting and abdominal pain can occur. Rapid i.v. injection may cause dizziness and hypotension; it is recommended that i.v. tranexamic acid is not administered faster than 100 mg min^{-1}.

Tranexamic acid should be avoided in those with a history of thromboembolic disease. Bleeding from the upper urinary tract is a contraindication because of the danger of ureteric clot colic and obstruction [24]. It is not contraindicated in pregnancy although the usual caution should be observed. A limited amount of tranexamic acid may be present in breast milk, and an antifibrinolytic effect is unlikely [25]. No teratogenic effect has been observed in animals and its use does not appear to increase the risk of thrombosis [26].

Blood products

General properties of a concentrate used for treatment of VWD There is a lack of consensus regarding the properties that are required to make a VWF-containing concentrate suitable for the treatment of VWD. It is often stated that the presence of HMW multimers is essential for the *in vivo* correction of the defect in primary haemostasis but this remains controversial [27]. Cryoprecipitate, for example, with a full complement of HMW multimers, does not consistently correct the bleeding time [28]. This is explicable given that the bleeding time is largely dependent on platelet VWF content. In practice, many VWF/FVIII concentrates available have proven clinical efficacy [29–31] in spite of lacking some HMW multimers [32,33]. The FVIII:C, VWF:Ag and VWF:RCo levels, and multimer structure of available concentrates have been reviewed [27].

Data is available *in vivo* from a crossover study on the ability of four concentrates to correct laboratory parameters [32]. This study demonstrated that Haemate-P (Aventis, King of Prussia, Pennsylvania, USA), BPL 8Y (Bio Products Laboratory, Elstree, UK), Alpha VIII and VHP-VWF had similar VWF:RCo recoveries of 2.1–2.4 IU mL^{-1} per IU kg^{-1} infused. There was a more consistent normalization of bleeding time with Haemate-P compared with the other concentrates but the bleeding time was shown not to correlate with the measured VWF:RCo. No concentrate completely normalized the VWF multimer structure *in vivo*.

There are no published data to suggest that differences in laboratory parameters (e.g. FVIII/VWF ratio, VWF multimer composition) between concentrates results in a difference in haemostatic efficacy. Furthermore, no studies have compared the clinical efficacy of concentrates.

Venous thromboembolism and replacement therapy for VWD Recently, cases of venous thromboembolism (VTE) have been described in patients with VWD who have been repeatedly treated with plasma concentrates, usually at short intervals. More than 10 cases have been described [34, 35]. Although none of the reported patients had evidence of inherited thrombophilia, many had specific risk factors for VTE such as surgery, hormonal therapy and immobility. In patients who had FVIII:C measured the majority had levels above the normal range, although this would not be unusual in an unaffected individual postsurgery as an acute phase response.

The mechanism for VTE is unknown. However, it is widely accepted that high FVIII is a risk factor for VTE, independent of VWF level and ABO blood group. As there is endogenous production of FVIII within the patient with VWD, concentrates that contain FVIII as well as VWF may lead to progressively increasing levels of FVIII, compared with the rises in VWF level. This is especially likely to be seen when dosing is solely based on labelled VWF:RCo potency without taking into account the variability of FVIII concentration relative to VWF in different concentrates.

On current evidence there is no reason to limit the use of replacement therapy with FVIII-VWF containing concentrates, but it would be advisable in patients undergoing prolonged treatment to measure FVIII:C levels daily to avoid levels of >100 U dL^{-1}. Thromboprophylaxis should be considered in the context of any proposed surgical interventions.

Recommendations

1 All concentrates used to treat patients with VWD should be virally inactivated (grade B, level III). In general a dual viral inactivation procedure is likely to offer greater protection against possible infection (grade C, level IV).
2 Because of current concerns about variant CJD (Creutzfeldt-Jakob Disease), concentrates manufactured from plasma from countries without

cases of variant CJD should be preferred (grade C, level IV).

3 In the absence of a good correlation between laboratory parameters and haemostatic effect, when selecting a concentrate for patients with VWD most reliance should be placed on studies that have demonstrated reproducible clinical efficacy (grade C, level IV).

Concentrates commonly used in the UK

In a survey of 25 large haemophilia centres in Europe and Japan the concentrates thought to be most useful for the management of VWD unresponsive to DDAVP were BPL 8Y, Haemate-P, Alphanate (Alpha Therapeutic Corporation, LA., California, USA) and VHP-VWF concentrate [36]. These concentrates are described in more detail below.

BPL 8Y

This is an intermediate purity FVIII concentrate. It is dry heated at 80 °C for 72 h. It is sourced from the USA plasma and licenced in the UK for the treatment of VWD. The amount of VWF:Ag per vial, as measured by enzyme-linked immunosorbent assay (ELISA), is on the label. The product data sheet states that 1 IU of VWF:Ag is associated with 0.8 IU VWF:RCo and 0.4 IU FVIII:C. The multimer structure of the concentrate is not identical to normal plasma with a lack of HMW multimers.

The manufacturers advise that in VWD the dose of 8Y should be calculated to achieve a target plasma level of FVIII (communication from BPL). Studies published on the clinical use of BPL 8Y report a satisfactory clinical response and correction of laboratory parameters associated with VWD [29,30].

Haemate-P

This is an intermediate purity FVIII concentrate. It is pasteurized at 60 °C for 10 h. It is made from German, Austrian and the USA plasma and licenced in the UK for prophylaxis and treatment of bleeding in VWD.

The concentrate contains about 2.5 IU VWF:RCo for each unit of FVIII:C [31]. The amount of VWF:RCo is printed on each vial. The summary of product characteristics states that the expected *in vivo* recovery is 1.5 IU dL^{-1} rise per IU kg^{-1} VWF:RCo administered. It is further stated that administration of 1 IU of FVIII kg^{-1} can be expected to lead to a rise in circulating VWF:RCo of approximately 3.5–4 IU dL^{-1}. Data has been presented demonstrating a multimer structure that shows a decrease in HMW multimers compared with normal plasma but better preservation of these multimers compared with some other concentrates [33].

A retrospective survey reported 97 patients with all types of VWD who were treated for 73 surgical operations, 344 bleeding events and 93 other events (invasive procedures and test doses). The efficacy was rated as excellent or good in 99% of surgical operations (including 21 type 3 VWD and 19 type 2 VWD), 97% for bleeding events and 86% of other events. In this study, the median *in vivo* recovery was 1.35 IU dL^{-1} VWF:RCo (range 0.36–2.98) for 1 IU VWF:RCo kg^{-1} infused [31]. There have been other smaller reports of good haemostatic efficacy of Haemate-P in both adults [37,38] and children [39].

Haemate-P has been used as a continuous infusion to cover surgical procedures, deliveries and bleeding episodes with good clinical efficacy [40].

Alphanate

Alphanate is a high purity FVIII concentrate containing VWF that is produced by affinity chromatography and salt/glycine precipitation. It is solvent/detergent and dry heat treated at 80 °C for 72 h. It is sourced from the USA plasma and is licenced in the UK for treatment of bleeding and prophylaxis of surgical bleeding in VWD. The concentrate contains approximately 0.6 IU VWF:RCo for each unit of FVIII:C [41]. The assayed VWF:RCo amount is printed on each vial for each lot. The multimer structure lacks HMW multimers when compared with plasma.

Alphanate has been the subject of a prospective study of treatment and prophylaxis in VWD using pre-established dosage regimens based on VWF:RCo [41]. VWD patients treated with Alphanate (and its predecessor ALPHA VIII) included 14 patients (three with type 1, seven with type 2A, four with type 3 VWD) who received 135 infusions for a total of 87 bleeding episodes. Prophylaxis of bleeding was reported in 39 patients (six with type 1, 17 with type 2A, two with type 2B, 14 with type 3 VWD) undergoing 71 surgical or invasive diagnostic procedures. In all cases adequate haemostasis was achieved, with none of the patients requiring the use of alternative blood products. Musculoskeletal and genitourinary bleeding required, on average, more treatments per bleeding episode and higher overall dosages. It was also demonstrated that surgery could be safely undertaken even when Alphanate did not correct the bleeding time.

Fanhdi (US plasma source), a similar product to Alphanate (Institute Grifols, Barcelona, Spain) is marketed in the UK by Grifols. Fanhdi has been reported to be efficacious in the management of VWD in a retrospective clinical study. In 22 patients 12 bleeding episodes and 14 invasive procedures were treated with Fanhdi. There was 92% excellent or good efficacy and no adverse events [42].

VHP-VWF concentrate

This is a high purity VWF concentrate prepared by ion-exchange chromatography from solvent–detergent-treated cryoprecipitate. It is sourced from French plasma and is licenced for the treatment of VWD only in France and Belgium (LFB, Lille, France). It has been used in the UK for this indication on a named patient basis. The VWF:RCo content is indicated on each vial. The multimer structure of the concentrate is well-preserved but not normal [43,44].

Clinical efficacy has been demonstrated in a review of 75 patients (including four with type 3 and 22 with type 2 VWD) [45]. Adequate haemostasis is reported after one infusion for epistaxis and minor bleeding. Gastrointestinal bleeding required infusions once or twice daily for a more prolonged period. The mean initial dosage given was 47 IU VWF:RCo kg^{-1}. Surgery was covered with an infusion, 1 h preoperatively in patients with FVIII:C >20 IU dL^{-1} (30 IU dL^{-1} for major surgery). A total of 31 minor and 23 major procedures were reported. The mean initial dose was 51–55 IU VWF:RCo kg^{-1}. The mean VWF:RCo in patients postinfusion was 100 IU dL^{-1} and the FVIII:C level was above 50 IU dL^{-1} in almost all patients. Patients with FVIII below 20–30 IU dL^{-1} received either one infusion of VHP-VWF concentrate given 12–24 h preoperatively, with a second infusion 1-h preoperatively, or one infusion of VHP-VWF concentrate and an infusion of FVIII 1-h preoperatively. The VWF:RCo was raised to >100 IU dL^{-1} for major surgery and the FVIII:C was >60 IU dL^{-1} in all patients. VWF:RCo was maintained at about 100 IU dL^{-1} for 1–16 days depending on the procedure. No further FVIII was required and all patients had adequate haemostasis.

The VHP-VWF concentrate has also been used successfully as a continuous infusion [46].

Platelets

The bleeding time in patients with VWD may be shortened by infusion of normal platelets even if there has been a poor response to replacement of VWF [47]. If mucosal bleeding persists and the bleeding time or PFA 100 closure time remains prolonged after adequate replacement therapy with a VWF containing concentrate, platelet infusions should be considered. Platelets from human leucocyte antigen (HLA) compatible donors should be used if repeated or frequent use is likely.

Cryoprecipitate

Cryoprecipitate available in the UK is sourced from the UK plasma. Whilst it will have been screened for the absence of markers of HIV, hepatitis B and C infection, it is not, however, virally inactivated. It should not, therefore, be used for the management of VWD unless other treatment modalities have failed [36]. Cryoprecipitate contains functionally active VWF with good preservation of multimer structure but does not consistently normalize the bleeding time [28]. Some patients who have not responded to VWF-containing concentrates may respond to cryoprecipitate.

Treatment of specific problems in VWD

Bleeding from the nose and mouth

Bleeding from the oral cavity, for example, gums, frenulum tears, bites of the lips and cheeks, are often seen, especially in young children. They may often be controlled by oral or topical (mouth wash) tranexamic acid. If not treatment with DDAVP- or VWF-containing concentrate is indicated.

Prolonged and frequent epistaxis is common in VWD. Oral tranexamic acid may be effective and for frequent cases nasal cautery can be effective. For severe bleeds DDAVP- or VWF-containing concentrate is needed.

Dental treatment

For fillings done under infiltration with local anaesthetic, treatment with DDAVP or concentrates is not needed. Treatment should be given if an inferior dental block is to be used (grade C, level IV). In responsive patients a single dose of DDAVP given with tranexamic acid is usually sufficient to cover dental extractions. Treatment should be monitored at least with a FVIII:C assay unless DDAVP has been shown to be effective on previous occasions. If DDAVP cannot be used a single dose of a VWF containing concentrate can be used aiming to achieve 50 IU dL^{-1} VWF:RCo.

Tranexamic acid should be given orally (starting before treatment) and/or as a mouthwash for 5 days afterwards [48].

Menorrhagia

Menorrhagia is very common in women with VWD [49] and conversely VWD is common in women presenting with menorrhagia [50,51]. Options for treatment include the combined oral contraceptive pill (COC), tranexamic acid, DDAVP and the intrauterine progestogen-only contraceptive (Mirena – Schering Plough) [52]. Although frequently listed as a treatment option, ethamsylate, at currently recommended doses, is not an effective treatment for menorrhagia [53].

In a retrospective survey 22 of 30 (73%) of women with VWD and menorrhagia had a good response to the COC [54], while tranexamic acid was shown to reduce menstrual blood loss by 50% [53,55] and is often successful in VWD. The usual dose of tranexamic acid has been 1 g qds for 4–5 days at the beginning of menstruation, although a small study found 4 g oral dose to be effective in four of four patients with VWD [56]. The oral therapies, tranexamic acid or the COC, are usually the first line treatments for menorrhagia. If they are not satisfactory DDAVP can be used at home either intranasaly or s.c. Subcutaneous DDAVP was found to be effective in 86% of treatments (43 menstrual cycles in 14 women) [57]. A maximum of three doses was advised. A study of intranasal DDAVP in 68 patients with type 1 VWD has been reported in abstract form – patients reported an excellent or good response on 92% of 552 treatment days [58]. Patients were treated on average for 1.8 days per cycle. As 90% of menstrual blood loss occurs in the first 3 days [59] and in view of the risk of water retention with prolonged administration of DDAVP we would recommend treatment once daily for 2–3 days.

Patients with heavy menorrhagia despite tranexamic acid, COC pill and DDAVP spray, should be referred to and managed in conjunction with a gynaecologist.

Pregnancy

During pregnancy VWF starts to rise as early as the sixth week and by the third trimester may have increased three- to fourfold so that many patients with type 1 VWD achieve VWF levels in the normal (non-pregnant) range. In type 2B VWD the increase in the abnormal VWF can cause thrombocytopenia but intervention is not usually required [60].

All women with VWD should be delivered in an obstetric unit, which can easily and quickly access the facilities of a Haemophilia Centre and comprehensive neonatal care facilities. A delivery plan should be drawn up jointly between the obstetrician and Haemophilia Centre. A close and continuing collaboration is required throughout the pregnancy and delivery. All women should be informed of the plans for the management of their pregnancy, risks of bleeding and risks to the fetus [61].

If the fetus is at risk of type 3 VWD the parents may wish to consider antenatal diagnosis. This should be planned in advance to allow the causative mutation(s) or informative polymorphisms to be identified.

In type 3 disease FVIII and VWF levels do not increase during pregnancy and VWF concentrates are required to cover delivery or caesarean section. In patients with types 1 and 2 VWD levels should be checked at 34–36 weeks, vaginal delivery is generally regarded as safe if VWF activity (VWF:RCo) is >40 IU dL^{-1}. VWF activity should be >50 IU dL^{-1} for caesarean section, if not DDAVP or VWF concentrates are needed. Treatment is likely to be required if a patient with type 2 VWD suffers a significant perineal tear or has an episiotomy. Even if VWF levels are satisfactory they may fall rapidly after delivery and DDAVP or VWF concentrates may be needed to treat postpartum haemorrhage. Women with symptomatic type 1 VWD may start to bleed abnormally at days 4–5. One should be aware of this risk and it would be, therefore, advisable to check VWF levels in women with VWD, particularly those with type 1 VWD and significantly low prepregnancy baseline levels, 3–5 days postpartum. This must also be considered in discharge planning to avoid severe bleeding occurring at home. All patients should be warned about the potential risk of bleeding following discharge.

Women delivered by caesarean section may require several treatments with VWF concentrates or DDAVP, sufficient to maintain haemostasis for at least 7 days. Patients with type 3 disease, delivered vaginally or by caesarean section, will require treatment with VWF concentrate for at least 7 days.

Although epidural anaesthesia for pain relief may be considered for use in the majority of women with type 1 VWD whose levels have risen to within the normal range during the pregnancy, it should not be undertaken lightly and without due consideration. In each case, before an epidural is used, consideration must be given haemostatic concerns such as the degree of correction of the plasma FVIII:C and VWF levels, possible degree of residual platelet impairment, possible rate of postpartum decline of VWF and consequent risks of bleeding/spinal haematoma. The issues need to be balanced against the obstetric indications for epidural anaesthesia in discussion with the relevant obstetrician and anaesthetist. When

considering use of an epidural or spinal anaesthetic for caesarean section these risks should be balanced against the risk of a general anaesthetic. In all cases an anaesthetist experienced in epidural anaesthesia should insert the epidural. Epidural anaesthesia is not recommended for use in types 2 or 3 VWD.

Where a fetus is at risk of having types 2 or 3 VWD, fetal scalp monitoring, rotational forceps and Ventouse delivery should be avoided. If a forceps or Ventouse procedure is performed there is a risk of intracranial bleeding. Irrespective of the mode of delivery, newborns at risk of types 2 or 3 VWD need to be tested for VWD using cord blood and assessed to exclude intracranial haemorrhage. For types 2A, 2B, 2M and 3 VWD the most rapid diagnostic approach is assay of ristocetin-induced platelet aggregation on a cord blood sample. For type 2N VWD a FVIII:C assay is required. If the child had a traumatic operative delivery and is shown to have types 2 or 3 VWD, early replacement therapy may be required. A haemophilia specialist should therefore be contacted immediately for advice on management. Cord blood screening for VWD will not give reliable results in type 1 disease.

Angiodysplasia and VWD

Angiodysplasia is reported in up to 6% of patients with VWD and may cause gastrointestinal haemorrhage [62,63]. The diagnosis can be made by endoscopy, isotope scanning or angiography. It is not thought there is a causal relationship, rather that the VWD probably unmasks the angiodysplasia. If angiodysplasia occurs in the stomach or duodenum then proton pump inhibitors may reduce bleeding. The value of hormonal therapies such as oestrogen treatment is not clear [64,65] although there is now some emerging evidence of the potential value of octreotide [66]. Local ablation at endoscopy with plasma-argon photocoagulation, or laser or heat coagulation can be effective. Surgical resection should be avoided if at all possible. In patients with recurrent severe bleeding prophylaxis with VWF containing concentrates may be effective.

Recommendations

1 Epistaxis and bleeding from the oral cavity often responds to tranexamic acid alone. If not DDAVP or VWF concentrate is needed (grade C, level IV).
2 A single dose of DDAVP given with tranexamic acid is sufficient for dental extractions in most patients. Otherwise a single dose of concentrate is usually sufficient (grade C, level IV).
3 Menorrhagia because of VWD can often be controlled with the COC pill (grade B, level III) or tranexamic acid (grade A, level Ib) or a combination of the two. If not s.c. or intranasal DDAVP should be considered (grade B, level IIb). A further option is the intra-uterine progestogen-only contraceptive device (grade C, level IV).
4 All women with VWD need to be delivered in a major obstetric unit (grade C, level IV). The haematologist and obstetrician will be required to collaborate closely to ensure safe antenatal, delivery and postnatal management.
5 In type 1 VWD treatment is not usually needed for delivery. If required, the treatment options are the same as in the non-pregnant although all drugs should be given with caution in pregnancy. If DDAVP is used then prolonged administration should be avoided and the patient monitored closely for water retention (grade C, level IV).
6 DDAVP should be avoided in women with pre-eclampsia (grade C, level IV).
7 In type 2 VWD treatment will be required if an episiotomy is performed to assist delivery, a perineal tear occurs or for other operative delivery (grade C, level IV).
8 Women with type 3 VWD require treatment for all types of delivery (grade C, level IV).

Management of surgery and other invasive procedures

Surgical procedures on patients with VWD require good liaison between an experienced haematologist and the surgical/anaesthetic team. It is essential that laboratory facilities to assay measure VWF:RCo and FVIII:C are available 24 h day^{-1}.

Haemostasis in patients with VWD who are undergoing invasive procedures requires the correction of the defect in VWF-platelet–vessel wall interactions and the deficiency of FVIII. Correction of the defect in VWF function is most important perioperatively and in the immediate postoperative period particularly when mucosal bleeding is possible. VWF activity is usually measured by VWF:RCo. This correlates poorly with the bleeding time or PFA 100 closure time. The FVIII level is an important determinant of surgical and soft tissue bleeding and therapeutic levels need to be maintained peri- and postoperatively for 7–10 days.

Strategies for the perioperative management of patients with VWD depend on the type of VWD, the baseline levels of VWF and FVIII, knowledge of the patient's past responses to DDAVP and the site and size of the planned procedure.

A regular clinical assessment of haemostasis is crucial but it is important to remember that abnormal bleeding may be surgical rather than due to a failure of adequate replacement therapy. Patients who bleed in spite of apparently adequate treatment should have a FBC, FVIII:C and VWF:RCo levels measured urgently and a bleeding time or PFA 100 closure time performed. In patients with type 3 VWD the development of an inhibitor to VWF needs to be considered and tested for. Patients with either low factor levels or a prolonged bleeding time or PFA 100 closure time should be treated with a further dose of FVIII/VWF concentrate. Therapeutic options where there has been a failure to correct the haemostatic defect include platelet infusion [47], DDAVP and cryoprecipitate [67].

Monitoring therapy

Prior knowledge of individual patient's responses to DDAVP and FVIII/VWF concentrate can be used to inform clinical decisions.

Factor VIII

It is standard practice to monitor the FVIII:C level in patients with VWD who are undergoing invasive procedures [36]. FVIII:C is, however, only a surrogate marker and does not necessarily reflect the VWF:RCo, particularly in patients with types 2 and 3 VWD or patients who have received FVIII/VWF containing concentrates. In these situations the VWF:RCo may be considerably lower than the FVIII:C.

VWF function

For major surgery in patients with VWD it has been recommended that VWF:RCo is monitored and treatment repeated to maintain a VWF:RCo level at about 100 IU dL^{-1} perioperatively and >50 IU dL^{-1} in the immediate postoperative period, until haemostasis is secure. There are no clear data that show a good correlation with this practice and surgical haemostasis [36].

It has also been recommended that therapy should aim to correct the bleeding time. A retrospective study of 76 patients unresponsive to DDAVP undergoing surgical procedures, however, showed no correlation between correction of the bleeding time and surgical haemostasis. Furthermore, clinicians did not alter their management dependent on the bleeding time result [68]. Correction of the bleeding time is thought to be more important in procedures where mucosal bleeding is likely but cannot be recommended as essential. It should be measured if patients are bleeding abnormally in spite of replacement therapy. Some patients whose bleeding time is not corrected with infused VWF may respond to platelet infusions [47].

Current practice

A survey of experienced clinicians reported that 22 of 24 responders measured the FVIII:C daily and 18 of 24 measured VWF:RCo daily. Only five of 24 monitored the bleeding time and two of these only on the first postoperative day [36]. This variability reflects the lack of evidence available.

Recommendations

1 Operative procedures on patients with VWD should be performed at a centre with clinicians experienced in the management of inherited bleeding disorders and with the appropriate laboratory facilities (grade C, level IV).
2 Operative procedures should be covered with DDAVP in responsive patients unless contraindicated (grade B, level III).
3 Patients who are unresponsive to DDAVP, or in whom it is contraindicated, should be treated with a virus-inactivated concentrate that contains either FVIII/VWF or VHP-VWF and which has been shown to be clinically effective (grade B, level III).
4 Operative procedures that involve mucosal surfaces should also be covered with tranexamic acid unless this is contraindicated (grade C, level IV).
5 Factor VIII levels should be monitored regularly in all major and most minor surgical procedures (grade B, level III). The FVIII:C plasma concentration should be about 100 IU dL^{-1} to cover major surgery and sustained above 50 IU dL^{-1} in the postoperative period (grade B, level III).
6 The VWF:RCo should be monitored in major surgical procedures particularly in the perioperative period (grade C, level IV). The VWF:RCo should be maintained above 50 IU dL^{-1} in the perioperative period (grade C, level IV).
7 Platelet infusions and DDAVP should be considered if bleeding occurs after adequate replacement therapy with a VWF containing concentrate (grade C, level IV).
8 Cryoprecipitate should not be used for the management of VWD unless other treatment modalities have failed. Some patients who have not responded to VWF containing concentrates may respond to cryoprecipitate (grade C, level IV).

Specific management options

Type 1 VWD

Most patients with type 1 VWD will respond to DDAVP to release sufficient VWF and FVIII to raise levels three- to fivefold [69].

Minor procedures Minor procedures on patients with type 1 VWD can usually be covered with DDAVP in responsive patients [69]. A single infusion of DDAVP is likely to be sufficient in many instances but some patients will require multiple infusions. The level of VWF:RCo and FVIII:C required and length of time this needs to be sustained will depend on the procedure being performed but perioperative levels above 50 IU dL^{-1} will almost certainly be sufficient.

The FVIII:C and VWF:RCo levels should be monitored following DDAVP unless this response is already well-known. In patients who require repeated infusions of DDAVP monitoring of the FVIII:C and, if necessary, VWF:RCo levels should be performed to ensure that tachyphylaxis has not occurred.

Major procedures Major procedures can be covered with DDAVP in patients who are known to be responsive. Perioperatively the VWF:RCo and FVIII:C levels should be maintained at or above 50 IU dL^{-1} until haemostasis has been secured. Thereafter, the FVIII:C level will need to be maintained above 50 IU dL^{-1} for 7–10 days. Monitoring should be at least daily to determine treatment frequency. Patients who are treated with DDAVP for more than 2 days must be monitored clinically and biochemically for evidence of fluid retention.

Patients who develop tachyphylaxis may need to be treated with a FVIII/VWF containing concentrate or VHP-VWF concentrate.

Patients who are known not to be responsive to DDAVP or in whom DDAVP is contraindicated should be treated with a FVIII/VWF containing concentrate or VHP-VWF concentrate as described below.

Types 2A or 2M VWD

Minor procedures Minor procedures may be covered with DDAVP in patients who have been shown to be responsive in a therapeutic trial [70]. FVIII:C and VWF:Ag levels are likely to be raised more in comparison with the VWF:RCo or correction of the bleeding time. The improvement in VWF:RCo or bleeding time may not be sustained. Laboratory monitoring should be performed with FVIII:C levels and VWF:RCo assay.

Patients who are not responsive to DDAVP will need to be treated with either a VWF/FVIII containing concentrate or a VHP-VWF concentrate. The level required postinfusion and the length of time this needs to be sustained depends on the procedure being performed. If VHP-VWF concentrate is used it must be given 12 h in advance (in patients with VWF:RCo below 20 IU dL^{-1}) to allow the endogenous FVIII level to increase or be given in association with a FVIII containing concentrate [45].

Major procedures The FVIII:C level should be raised to about 100 IU dL^{-1} perioperatively and maintained above 50 IU dL^{-1} for 7–10 days. In addition, the VWF:RCo should be maintained at or above 50 IU dL^{-1} until haemostasis is secure. This may be required for a more prolonged period if mucosal surfaces are involved when it is likely that treatment with FVIII/VWF or VHP-VWF concentrate will be required.

Type 2B VWD

In general, management should be with FVIII/VWF containing concentrate or VHP-VWD as indicated for types 2A or 2M VWD.

It is the opinion of many clinicians that DDAVP is contraindicated in patients with type 2B VWD as a result of the risk of thrombocytopenia. There are a few reports where this treatment has been used safely [19]. If DDAVP is used the platelet count should be monitored.

Type 2N VWD

Treatment with DDAVP will increase the level of FVIII to normal in most patients. The half-life of the FVIII, however, will be significantly reduced and should be monitored regularly. The VWF:RCo and bleeding time or PFA 100 closure time do not need to be monitored.

Minor procedures Minor procedures can often be performed under DDAVP cover with tranexamic acid as adjunctive therapy.

Major procedures Procedures that require a prolonged correction of the FVIII level are unlikely to be possible using DDAVP alone. FVIII/VWF containing concentrates will normalize the half-life of endogenous FVIII. Raising the FVIII:C level to about 100 IU dL^{-1}

perioperatively and maintaining it above 50 IU dL^{-1} for 7–10 days will provide adequate cover for major procedures. The improved half-life of FVIII means that once daily treatment is usually sufficient.

The FVIII:C level can also be normalized with a VHP-VWF concentrate. Patients who have a FVIII:C >30 IU dL^{-1} (20 IU dL^{-1} for a minor procedure) may be treated 1 h before an elective procedure with VHP-VWF concentrate alone. Patients with lower FVIII:C levels will require treatment 12–24 and 1 h before a procedure. Emergency procedures that require urgent correction of haemostasis may be treated with VHP-VWF concentrate and a FVIII concentrate. In all cases, the FVIII:C level should be monitored regularly [45].

Type 3 VWD

Patients undergoing invasive procedures will need to be treated with a VWF containing concentrate. It is generally agreed that the FVIII:C level and VWF:RCo should be raised to about 100 IU dL^{-1} perioperatively and maintained at or above 50 IU dL^{-1} for 7–10 days.

Factor VIII:C and VWF:RCo levels can also be normalized using VHP-VWF concentrate. Patients will require treatment 12–24 h preoperatively (aiming to correct the VWF:RCo to about 100 IU dL^{-1}) and also 1 h before the procedure. Emergency procedures that require urgent correction of haemostasis must be treated with VHP-VWF concentrate and a FVIII concentrate. In all cases, FVIII:C and VWF:RCo levels should be monitored [45].

An alternative approach is to use a continuous infusion of either a VWF/FVIII containing concentrate or a VHP-VWF concentrate. This strategy results in a good correction of the haemostatic defect of VWD and has been shown to be clinically effective in type 3 VWD [40,46]. It may also lead to a decrease in the amount of FVIII/VWF used [40]. It should be noted, however, that no product is licenced for use as a continuous infusion in VWD.

Minor procedures will require replacement of VWF and FVIII but, depending on the type and site of the procedure, the required levels may not need to be so high or treatment so prolonged.

Surgery in patients with an inhibitor to VWF Inhibitors may occur in type 3 VWD. Only limited experience in their management is available. Where invasive procedures cannot be avoided patients should be managed at a Comprehensive Care Centre experienced in the management of patients with inhibitors of haemostasis. Patients are at risk of anaphylactic reactions to VWF containing concentrates. There is very limited experience reported in the literature but recombinant VIIa (rVIIa) [71] and continuous infusion of high doses of rFVIII [72] have been successfully used.

Acquired von Willebrand syndrome

Acquired von Willebrand syndrome (AVWS) is a complex disorder with a multiple aetiologies that lead to low levels of VWF [73]. It is, therefore, difficult to give clear treatment guidelines for this condition. Patients with identified AVWS should be referred to a Comprehensive Care Centre for management of any bleeding episodes.

Treatment of the underlying condition may result in VWF levels improving or returning to normal. If this is not so and bleeding occurs or surgery is planned then VWF containing concentrates may be used, but in many cases the responses to these infusions will be relatively short. Similarly, the use of DDAVP may lead to only transient responses. In cases due to an autoantibody, i.v. immunoglobulins may restore normal levels for several days. Plasma exchange or immunoabsorption could also be considered.

Note on nomenclature

The nomenclature used for VWF and its properties is that recommended by the VWF Subcommittee of the Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis (http://www.med.unc.edu/isth/vwf2.htm)

Attribute	Recommended abbreviations
Mature protein	VWF
Ristocetin cofactor activity	VWF:RCo
Antigen	VWF:Ag
Collagen-binding capacity	VWF:CB
Factor VIII-binding capacity	VWF:FVIIIB
Factor VIII coagulant activity	FVIII:C

Disclaimer

The information and advice contained within this guideline are believed to be true and accurate at the time of going to press. Neither the authors nor the publishers can accept any legal responsibility for any errors or omissions that may have occurred.

Declarations of interest

All members of the Executive of the UKHCDO and UKHCDO Working Party members are obliged to

present a declaration of interests to the Chairman of the UKHCDO annually. None of the authors has any shareholding in any pharmaceutical company, None of the authors is acting as an advisor or consultant for any of the manufacturers in relation to products currently used for the treatment of VWD.

References

1 Sadler JE. A revised classification of von Willebrand disease. *Thromb Haemost* 1994; **71**: 520–25.

2 UK Haemophilia Centre Doctors' Organisation von Willebrand Disease Working Party. Guidelines for the diagnosis and management of von Willebrand disease. *Haemophilia* 1997; **3** (Suppl. 2): 4–8.

3 Mannucci PM, Cattaneo M. Desmopressin: a non-transfusional treatment of hemophilia and von Willebrand disease. *Haemostasis* 1992; **22**: 276–80.

4 Mazurier C, Gaucher C, Jorieux S, Goudemand M. Biological effect of desmopressin in eight patients with type 2N ('Normandy') von Willebrand disease. Collaborative Group. *Br J Haematol* 1994; **88**: 849–54.

5 De Sio L, Mariani G, Muzzuconi MG, Chistolini A, Tirindelli MC, Mandelli F. Comparison between subcutaneous and intravenous DDAVP in mild and moderate hemophilia A. *Thromb Haemost* 1985; **54**: 387–9.

6 Lethagen S, Harris AS, Sjorin E, Nilsson M. Intranasal and intravenous administration of desmopressin: effect on F VIII/vWF, pharmacokinetics and reproducibility. *Thromb Haemost* 1987; **58**: 1033–6.

7 Lethagen S, Ragnarson Tennvall G. Self-treatment with desmopressin intranasal spray in patients with bleeding disorders: effect on bleeding symptoms and socioeconomic factors. *Ann Hematol* 1993; **66**: 257–60.

8 Dunn AL, Powers JR, Ribeiro MJ, Rickles FR, Abshire TC. Adverse events during use of intranasal desmopressin for haemophilia A and von Willebrand disease: a case report and review of 40 patients. *Haemophilia* 2000; **6**: 11–4.

9 Holmberg L, Nilsson IM, Borge L, Gunnarsson M, Sjorin E. Platelet aggregation induced by 1-desamino-8-D-arginine vasopressin (DDAVP) in type IIB von Willebrand's disease. *N Engl J Med* 1983; **309**: 816–21.

10 Casonato A, Fabris F, Girolami A. Platelet aggregation and pseudothrombocytopenia induced by 1-desamino-8- D-arginine vasopressin (DDAVP) in type IIB von Willebrand's disease patient. *Eur J Hematol* 1990; **45**: 36–42.

11 Casonato A, Sartori MT, de Marco L, Girolami A. 1-Desamino-8-D-arginine vasopressin (DDAVP) infusion in type IIB von Willebrand's disease: shortening of bleeding time and induction of a variable pseudothrombocytopenia. *Thromb Haemost* 1990; **64**: 117–20.

12 Casonato A, Pontara E, Dannhaeuser D *et al.* Re-evaluation of the therapeutic efficacy of DDAVP in type IIB von Willebrand's disease. *Blood Coag Fibrinol* 1994; **5**: 959–64.

13 Casonato A, Steffan A, Pontara E *et al.* Post-DDAVP thrombocytopenia in type 2B von Willebrand disease is not associated with platelet consumption: failure to demonstrate glycocalicin increase or platelet activation. *Thromb Haemost* 1999; **81**: 224–8.

14 Fowler WE, Berkowitz LR, Roberts HR. DDAVP for type IIB von Willebrand disease. *Blood* 1989; **74**: 1859–60.

15 McKeown LP, Connaghan G, Wilson O, Hausmann K, Merryman P, Gralnick HR. 1-Desamino-8-arginine-vasopressin corrects the hemostatic defects in type 2B von Willebrand's disease. *Am J Hematol* 1996; **51**: 158–63.

16 Castaman G, Rodeghiero F. Desmopressin and type IIB von Willebrand disease. *Haemophilia* 1996; **2**: 73–7.

17 Bond L, Bevan D. Myocardial infarction in a patient with hemophilia treated with DDAVP. *N Engl J Med* 1988; **318**: 121.

18 Lowe GD. Desmopressin and myocardial infarction. *Lancet* 1989; **1**: 895–6.

19 McLeod BC. Myocardial infarction in a blood donor after administration of desmopressin. *Lancet* 1990; **336**: 1137–8.

20 Grunwald Z, Sather SD. Intraoperative cerebral infarction after desmopressin administration in infant with end-stage renal disease. *Lancet* 1995; **345**: 1364–5.

21 Ray JG. DDAVP use during pregnancy: an analysis of its safety for mother and child. *Obstet Gynecol Surg* 1998; **53**: 450–5.

22 Smith TJ, Gill JC, Ambruso DR, Hathaway WE. Hyponatremia and seizures in young children given DDAVP. *Am J Hematol* 1989; **31**: 199–202.

23 Sutor AH. DDAVP is not a panacea for children with bleeding disorders. *Br J Haematol* 2000; **108**: 217–27.

24 Fernandez Lucas M, Liano F, Navarro JF, Sastre JL, Quereda C, Ortuno J. Acute renal failure secondary to antifibrinolytic therapy. *Nephron* 1995; **69**: 478–9.

25 British National Formulary. William Clowes, Suffolk, 2002; **44**: 714.

26 Lindoff C, Rybo G, Astedt B. Treatment with tranexamic acid during pregnancy, and the risk of thromboembolic complications. *Thromb Haemost* 1993; **70**: 238–40.

27 Menache D, Aronson DL. New treatments of von Willebrand disease: plasma derived von Willebrand factor concentrates. *Thromb Haemost* 1997; **78**: 566–70.

28 Mannucci PM, Moia M, Rebulla P, Altieri D, Monteagudo J, Castillo R. Correction of the bleeding time in treated patients with severe von Willebrand disease is not solely dependent on the normal multimeric structure of plasma von Willebrand factor. *Am J Hematol* 1987; **25**: 55–65.

29 Cumming AM, Fildes S, Cumming IR, Wensley RT, Redding OM, Burn AM. Clinical and laboratory evaluation of National Health Service factor VIII

concentrate (8Y) for the treatment of von Willebrand's disease. *Br J Haematol* 1990; **75**: 234–9.
30 Pasi KJ, Williams MD, Enayat MS, Hill FG. Clinical and laboratory evaluation of the treatment of von Willebrand's disease patients with heat-treated factor VIII concentrate (BPL 8Y). *Br J Haematol* 1990; **75**: 228–33.
31 Dobrkovska A, Krzensk U, Chediak JR. Pharmacokinetics, efficacy and safety of Humate-P in von Willebrand disease. *Haemophilia* 1998; **4** (Suppl. 3): 33–9.
32 Mannucci PM, Tenconi PM, Castaman G, Rodeghiero F. Comparison of four virus-inactivated plasma concentrates for treatment of severe von Willebrand disease: a cross-over randomized trial. *Blood* 1992; **79**; 3130–7.
33 Metzner HJ, Hermentin P, Cuesta-Linker T, Langner S, Muller HG, Friedebold J. Characterization of factor VIII/von Willebrand factor concentrates using a modified method of von Willebrand factor multimer analysis. *Haemophilia* 1998; **4** (Suppl. 3): 25–32.
34 Makris M, Colvin B, Gupta V, Shields ML, Smith MP. Venous thrombosis following the use of intermediate purity FVIII concentrate to treat patients with von Willebrand's disease. *Thromb Haemost* 2002; **88**: 387–8.
35 Mannucci PM. Venous thromboembolism in von Willebrand disease. *Thromb Haemost* 2002; **88**: 378–9.
36 Lusher JM. Clinical guidelines for treating von Willebrand disease patients who are not candidates for DDAVP – a survey of European physicians. *Haemophilia* 1998; **4** (Suppl. 3): 11–4.
37 Berntorp E, Nilsson IM. Use of a high-purity factor VIII concentrate (Hemate-P) in von Willebrand's disease. *Vox Sang* 1989; **56**: 212–7.
38 Scharrer I, Vigh T, Aygoren-Pursun E. Experience with Haemate-P in von Willebrand's disease in adults. *Haemostasis* 1994; **24**: 298–303.
39 Kreuz W, Mentzer D, Becker S, Scharrer I, Kornhuber B. Haemate-P in children with von Willebrand's disease. *Haemostasis* 1994; **24**: 304–10.
40 Lubetsky A, Schulman S, Varon D *et al.* Safety and efficacy of continuous infusion of a combined factor VIII-von Willebrand factor (vWF) concentrate (Haemate-P™) in patients with von Willebrand disease. *Thromb Haemost* 1999; **81**: 229–33.
41 Mannucci PM, Chediak J, Hanna W *et al.* Treatment of von Willebrand disease with a high-purity factor VIII/von Willebrand factor concentrate: a prospective, multicenter study. *Blood* 2002; **99**: 450–6.
42 Federici AB, Baudo F, Caracciolo C *et al.* Clinical efficacy of highly purified, doubly virus-inactivated factor VIII/von Willebrand factor concentrate (Fanhdi) in the treatment of von Willebrand disease: a retrospective clinical study. *Haemophilia* 2002; **8**: 761–7.
43 Mazurier C, de Romeuf C, Parquet-Gernez A, Jorieux S, Goudemand M. In vitro and in vivo evaluation of a factor VIII concentrate heat-treated to inactivate HTLV-III/LAV viruses. Favourable effects of heating on the von Willebrand factor. *Vox Sang* 1987; **52**: 265–71.
44 Mazurier C, De Romeuf C, Parquet-Gernez A, Goudemand M. *In vitro* and *in vivo* characterization of a high-purity, solvent/detergent-treated factor VIII concentrate: evidence for its therapeutic efficacy in von Willebrand's disease. *Eur J Haematol* 1989; **43**: 7–14.
45 Goudemand J, Negrier C, Ounnoughene N, Sultan Y. Clinical management of patients with von Willebrand's disease with a VHP vWF concentrate: the French experience. *Haemophilia* 1998; **4** (Suppl. 3): 48–52.
46 Smith MP, Rice KM, Bromidge ES *et al.* Continuous infusion therapy with very high purity von Willebrand factor concentrate in patients with severe von Willebrand disease. *Blood Coag Fibrinol* 1997; **8**: 6–12.
47 Castillo R, Monteagudo J, Escolar G, Ordinas A, Magillon M, Martin Villar J. Hemostatic effect of normal platelet transfusion in severe von Willebrand disease patients. *Blood* 1991; **77**: 1901–5.
48 Sindet-Pedersen S. Haemostasis in oral surgery–the possible pathogenetic implications of oral fibrinolysis on bleeding. Experimental and clinical studies of the haemostatic balance in the oral cavity, with particular reference to patients with acquired and congenital defects of the coagulation system. *Dan Med Bull* 1991; **38**: 427–43.
49 Kadir RA, Economides DL, Sabin CA, Pollard D, Lee CA. Assessment of menstrual blood loss and gynaecological problems in patients with inherited bleeding disorders. *Haemophilia* 1999; **5**: 40–8.
50 Edlund M, Blomback M, von Schoultz B, Andersson O. On the value of menorrhagia as a predictor for coagulation disorders. *Am J Hematol* 1996; **53**: 234–8.
51 Kadir RA, Economides DL, Sabin CA, Owens D, Lee CA. Frequency of inherited bleeding disorders in women with menorrhagia. *Lancet* 1998; **351**: 485–9.
52 Lahteenmaki P, Haukkamaa M, Puolakka J *et al.* Open randomised study of use of levonorgestrel releasing intrauterine system as alternative to hysterectomy. *BMJ* 1998; **316**: 1122–6.
53 Bonnar J, Sheppard BL. Treatment of menorrhagia during menstruation: randomised controlled trial of ethamsylate, mefenamic acid, and tranexamic acid. *BMJ* 1996; **313**: 579–82.
54 Foster PA. The reproductive health of women with von Willebrand Disease unresponsive to DDAVP: results of an international survey. On behalf of the Subcommittee on von Willebrand Factor of the Scientific and Standardization Committee of the ISTH. *Thromb Haemost* 1995; **74**: 784–90.
55 Preston JT, Cameron IT, Adams EJ, Smith SK. Comparative study of tranexamic acid and norethisterone in the treatment of ovulatory menorrhagia. *Br J Obstet Gynaecol* 1995; **102**: 401–6.
56 Ong YL, Hull DR, Mayne EE. Menorrhagia in von Willebrand disease successfully treated with single daily dose tranexamic acid. *Haemophilia* 1998; **4**: 63–5.
57 Rodeghiero F, Castaman G, Mannucci PM. Prospective multicenter study on subcutaneous concentrated desmopressin for home treatment of patients with von

Willebrand disease and mild or moderate hemophilia A. *Thromb Haemost* 1996; **76**: 692–6.
58 Kobrinsky N, Goldsmith J. Efficacy of Stimate (desmopressin acetate) nasal spray, 1.5 mg ml^{-1}, for the treatment of menorrhagia in women with inherited bleeding disorders. *Blood* 1997; **90** (Suppl. 1): 106.
59 Janssen CA, Scholten PC, Heintz AP. A simple visual assessment technique to discriminate between menorrhagia and normal menstrual blood loss. *Obstet Gynecol* 1995; **85**: 977–82.
60 Giles AR, Hoogendoorn H, Benford K. Type IIB von Willebrand's disease presenting as thrombocytopenia during pregnancy. *Br J Haematol* 1987; **67**: 349–53.
61 Hill FG. Haematological disorders. *Clin Obstet Gynaecol* 1982; **9**: 75–90.
62 Fressinaud E, Meyer D. International survey of patients with von Willebrand disease and angiodysplasia. *Thromb Haemost* 1993; **70**: 546.
63 Ramsay DM, Buist TA, Macleod DA, Heading RC. Persistent gastrointestinal bleeding due to angiodysplasia of the gut in von Willebrand's disease. *Lancet* 1976; **2**: 275–8.
64 Lavabre Bertrand T, Navarro M, Blanc P, Larrey D, Michel H, Rouanet C. Von Willebrand's disease, digestive angiodysplasia, and estrogen-progesterone treatment. *Am J Hematol* 1994; **46**: 254–5.
65 Hodgson H. Hormonal therapy for gastrointestinal angiodysplasia. *Lancet* 2002; **359**: 1630–1.
66 Orsi P, Guatti-Zuliani C, Okolicsanyi L. Long-acting octreotide is effective in controlling rebleeding angiodysplasia of the gastrointestinal tract. *Dig Liver Dis* 2001; **33**: 330–4.
67 Cattaneo M, Moia M, Delle Valle P, Castellana P, Mannucci PM. DDAVP shortens the prolonged bleeding times of patients with severe von Willebrand disease treated with cryoprecipitate. Evidence for a mechanism of action independent of released von Willebrand factor. *Blood* 1989; **74**: 1972–5.
68 Foster PA. A perspective on the use of FVIII concentrates and cryoprecipitate prophylactically in surgery or therapeutically in severe bleeds in patients with von Willebrand disease unresponsive to DDAVP: results of an international survey. On behalf of the Subcommittee on von Willebrand Factor of the Scientific and Standardization Committee of the ISTH. *Thromb Haemost* 1995; **74**: 1370–8.
69 Mannucci PM. Desmopressin (DDAVP) in the treatment of bleeding disorders: the first 20 years. *Blood* 1997; **90**: 2515–21.
70 Gralnick HR, Williams SB, McKeown LP *et al.* DDAVP in type IIa von Willebrand's disease. *Blood* 1986; **67**: 465–8.
71 Ciavarella N, Schiavoni M, Valenzano E, Mangini F, Inchingolo F. Use of recombinant factor VIIa (NovoSeven) in the treatment of two patients with type III von Willebrand's disease and an inhibitor against von Willebrand factor. *Haemostasis* 1996; **26** (Suppl. 1): 150–4.
72 Federici A, Mannucci P. Diagnosis and management of von Willebrand disease. *Haemophilia* 1999; **5** (Suppl. 2): 28–37.
73 Veyradier A, Jenkins CSP, Fressinaud E, Meyer D. Willebrand Syndrome: from pathophysiology to management. *Thromb Haemost* 2000; **4**: 175–82.
74 AHCPR. *Acute Pain Management: Operative or Medical Procedures and Trauma*. Washington: Agency of Health Care Policy and Research Publications. United States Department of Health and Human Services, 1992.

Appendix: Note on recommendations

Grade of recommendation

Grade	Evidence	Recommendation level
A	Ia, Ib	Required – at least one randomized controlled trial as part of the body of literature of overall good quality and consistency addressing specific recommendation
B	IIa, IIb, III	Required – availability of well-conducted clinical studies but no randomized clinical trials on the topic of recommendation
C	IV	Required – evidence obtained from expert committee reports or opinions and/or clinical experiences of respected authorities
		Indicates absence of directly applicable clinical studies of good quality

Derived from the USA Agency for Health Care Policy and Research [74].

Level of evidence

Level	Type of evidence
Ia	Evidence obtained from meta-analysis of randomized controlled trials
Ib	Evidence obtained from at least one randomized controlled trial
IIa	Evidence obtained from at least one well-designed controlled study without randomization
IIb	Evidence obtained from at least one other type of well-designed quasi-experimental study
III	Evidence obtained from well-designed non-experimental descriptive studies, such as comparative studies, correlation studies and case–control studies
IV	Evidence obtained from expert committee reports or opinions and/or clinical experiences of respected authorities