

# More about...

## Haemophilia emergencies

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## Haemophilia in general

Classic haemophilia is an X-linked disorder, with either a deficiency of factor VIII (haemophilia A), or of factor IX (haemophilia B) being inherited from the mother. Factor VIII and IX, together with phospholipid, form the tenase complex which converts factor X to its active form Xa; deficiency of one is clinically indistinguishable from the other, and the diagnosis is made on blood levels. This level also serves to categorise the severity, with a factor level of < 1% being severe, 1 - 5% moderate and 5 - 25% mild. The severe and moderately affected individuals are prone to spontaneous bleeding - usually in joints - for which most patients are on home factor replacement therapy. They may, however, also present with spontaneous life-threatening bleeds; inappropriate iatrogenic intervention may also be responsible for this situation. For this reason, the emergency poster (Fig. 1) has been prepared and will be widely distributed to emergency units. This accompanying commentary will highlight certain features of this poster.

### Why factor first?

This is a recognition that most emergencies in severe or moderate haemophiliacs are likely to be related to bleeding, and that not only is early factor replacement more effective and may require a lower dose to control bleeding (note: these are expensive products), but delay will also allow further potential complications to develop, which may have been avoided had therapy been initiated earlier.

### Do's

- Most people living with haemophilia (PWH) or their families will not only know their diagnosis, but also their severity level and may be far more aware than the practitioner of not only the significance of certain symptoms, but also the need to give factor urgently. This, as is the case in rare disorders, should not lead the medical practitioner to dismiss the input of the PWH or their family as interfering with their autonomy, but rather to utilise the unique knowledge that these people may have acquired. It is, however, also a mistake to assume that all PWH or their families are fully informed about the condition, and each case should be treated on its merits.

- Most patients should be wearing a Medic-Alert identification, which will enable appropriate factor therapy if they are not aware of which factor is deficient. In any event, most experienced physicians, paediatricians or haemophilia nursing practitioners know their patient base, and are approachable for information regarding the diagnosis, complications and best treatment options for each PWH.

- PWH who have developed high titre inhibitors (most often severe factor VIII-deficient individuals) represent a difficult therapeutic challenge. Specialised 'bypass' therapies such as FEIBA or Novoseven have been developed, and require highly specialised input as they are extremely expensive, and may not be effective if given incorrectly. Certain PWH may be on home therapy with these products, but would be the one exception to the rule of factor first if presenting with ongoing symptoms. Urgent consultation with an experienced physician is required.

### Don'ts

- Do not ignore minor complaints - the patient with the intracerebral haemorrhage noted in Fig. 2 presented with a mild headache progressive over 2 days, but was ignored, which ultimately lead to his death. In fact, head bleeds are notorious for subtle presentation, and a very low threshold for CT scanning is indicated (with careful review as the radiological signs may be extremely subtle).
- Do not check levels - factor VIII or IX levels are genetically determined, and do

**Table I. Emergency contact numbers at comprehensive haemophilia care centres**

Town	Hospital	Physician	Phone
Bloemfontein	Universitas Hospital	D Stones	051 4053323
		MJ Coetzee	051 405 2136
Cape Town	Red Cross Children's	F Desai	021 658 5185
	Groote Schuur	A Mc Donald	021 404 9111/3497
	Tygerberg	G Wessels	021 9384564
Durban	King Edward VIII	Sr P Nkosi	083 265 5248
East London	Frere Hospital	R Mathew	043 709 2370
Johannesburg	Johannesburg	R Schwyzer	083 458 0845
		J Mahlangu	082 809 5806
	Chris Hani Baragwaneth	M Patel	011 933 8220/8000
Mthatha	Nelson Mandela Academic	B Ogunsanwo	084 321 2482
Polokwane	Pietersburg/ Mankweng	C Sutton	082 800 6778
Port Elizabeth	Dora Nginza	R Mitchel	041 406 4111
	PE Provincial	N Littleton	084 444 5087
Pretoria	Pretoria Academic	J Opperman	012 354 1000

# HAEMOPHILIA EMERGENCIES

## FACTOR FIRST

- **ASK IF** the symptoms could be caused by a bleed?
- If **YES TREAT** with **FACTOR FIRST** before investigating
- Check if **Haemophilia A** (factor 8 deficiency) or **B** (factor 9 deficiency)
- **ASK** the patients or families for help/information regarding diagnosis
- Treat with **appropriate** factor replacement therapy
- Check **MedicAlert®**
- Check for history of **INHIBITORS**
- Call **Haematologist** for known inhibitor patients
- Contact the **REGULAR** haemophilia doctor or sister for treatment protocol

- **Don't IGNORE** "MINOR" complaints which are not resolving
- **Don't CHECK** levels in patients with established diagnosis unless they are not responding to factor therapy
- **Don't WAIT** for results prior to commencing factor therapy
- **Don't sample Arterial blood**
- **Don't attempt** surgical intervention without factor replacement and recent inhibitor level
- **Don't give INTRAMUSCULAR** injections
- **Don't give ASPIRIN / NSAIDS**
- **Don't ASPIRATE** joints to diagnose bleeds

### MAJOR BLEED (without inhibitors)

- **Suspected Head / Brain, Retropharyngeal, Retroperitoneal, Fractures, Major Trauma, GIT, muscle bleeds, Limb compartment syndrome - TREAT 40 iu/ kg Factor 8 or 9 IMMEDIATELY**
- **INVESTIGATE AFTERWARDS**

### MINOR BLEED (without inhibitors)

- **Recent Haemarthrosis (joint bleed) Minor epistaxis (nose bleeds), Gum bleeds, Minor Trauma - TREAT 25 iu/kg Factor 8 or 9**
- **Mild von Willebrand disease / Mild Haemophilia A - TREAT with DDAVP 0.3 µg/kg if patient is a documented responder to DDAVP**

### ADJUNCTIVE THERAPIES

- **IMMOBILISE** joint **REST/ ICE** 5 minutes on 10 minutes off
- **Tranexamic acid** (contraindicated in urinary bleeds)

### INHIBITOR THERAPY rFVIIa or aPCC

- **REST, ICE, IMMOBILISE**
- **Urgently contact** the Patient's regular doctor

### CONTACT HAEMOPHILIA CENTRE:



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Fig. 1. Emergency poster for haemophilia.

## More about...



Fig. 2. Patient with intracerebral haemorrhage.

not fluctuate in severe or moderate PWH. It only delays time to effective therapy if the level is first measured to check if the patient still has haemophilia. There are, however, two potential causes for PWH not to respond to factor therapy, namely ongoing surgical type bleeding, which would require control by physical means (as in normal individuals); or the development of newly acquired antibodies (or inhibitors) to the factor therapy. In this situation, it would be advisable to measure factor levels post infusion.

- Do not sample arterial blood – many PWH have poor venous access and it is tempting to perform arterial venepunctures to obtain blood samples. This has a high complication rate in untreated PWH.

- Surgical interventions without factor therapy may appear to be feasible, as there is usually not an increased haemorrhage rate in theatre, as an initial fibrin clot may be formed. However, this is of poor quality, and is susceptible to rapid fibrinolysis, with resumption of bleeding, which is ongoing. Subsequent haematoma formation, wound infection and poor healing contribute to a massive increase in factor requirement compared with appropriate initial therapy, at considerable extra cost.

- Intramuscular infections have a high rate of haematoma formation, and should be avoided.

- Aspirin and most NSAIDs interfere with platelet function – they are inappropriate agents for analgesia in the acute setting with pain associated with a haemorrhage.

## Conclusion

Haemorrhage is a frequent occurrence in PWH; as these disorders are not common, many doctors and nurses do

not have experience in management, and trivial symptoms should not be ignored. Consultation with a more experienced physician is advised.

Contact details for the major haemophilia centers and units are found in Table 1.

## Menorrhagia and inherited bleeding disorders

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Women bleed – and this is especially so in childbearing years where menstruation and childbirth represent significant haemostatic challenges. Up to 10 - 15% of women will experience menorrhagia in their lifetime – either as primary (present from menarche) or secondary (developing later in life).

While the majority of excess bleeds are not related to haematological disorders, in certain series, bleeding diatheses accounted for 5 - 20% of underlying causes. These may be acquired (low platelets in patients with idiopathic thrombocytopenic purpura (ITP), antiplatelet drugs) or inherited bleeding disorders such as:

- von Willebrand disease (vWD)
- inherited platelet dysfunction disorders
- haemophilia A or B carrier status
- other rare factor deficiencies.

vWD is the most commonly reported diagnosis in most series, but the exact percentage varies according to the population studied and the number (and sensitivity) of the diagnostic tests employed (see below.)

Conversely, menorrhagia is a common presenting symptom of inherited disorders (up to 90% symptom prevalence in vWD). This is more likely to be primary, but secondary menorrhagia does not exclude the presence of an inherited disorder. A bleeding disorder is more likely if there is a history of increased haemorrhage at other

sites (see the article on von Willebrand disease for the assessment of bleeding.)

Menorrhagia may interfere significantly with quality of life and lead to complications such as iron deficiency as well as increased rates of procedures such as hysterectomy (with potential postoperative complications in an undiagnosed bleeder). Other complications in women with these disorders include an increased risk of endometriosis, endometrial polyps and haemorrhagic ovarian cysts. Thus the burden of morbidity of undiagnosed bleeding disorders is likely to be large.

## Obstacles to diagnosis

- Menorrhagia, while defined objectively as bleed volume of more than 80 ml per month, remains a very subjective experience, and may be under-estimated (or over-) by both patient and caregivers. This problem may be abrogated by the validation of pictorial assessment bleeding charts.

- Most causes of menorrhagia are not related to haematological disorders, and considerable costs may be incurred in fruitless investigations. The incidence of diagnosis is, however, related to the number of tests performed, and practitioners who claim that they do not see any cases are likely to be undertesting.

- The tests are either not sensitive enough (bleeding time), or variable/difficult to interpret (von Willebrand assays), or not widely available/expensive (platelet aggregometry, PFA-100) or combinations of the above problems (genotype-phenotype correlations difficult.)

## Management

It may well be asked whether making a diagnosis will affect management, as many of the strategies employed in patients with bleeding diatheses are similar to those employed for those who do not suffer from these disorders. This may even be true for patients who undergo surgical procedures with minimal excess bleeding – and particularly true of delivery in patients with haemophilia A carriage or type vWD, where factor VIII and vWF levels increase progressively with pregnancy duration,

**Menorrhagia may interfere significantly with quality of life and lead to complications such as iron deficiency as well as increased rates of procedures such as hysterectomy.**

and delivery may be uncomplicated (although levels drop postpartum and delayed haemorrhage may result.)

However, as many of these disorders have variable penetrance and fluctuate in an individual woman over time it should be noted that:

- one uncomplicated haemostatic stress event may not predict a future uncomplicated event – note that this is not well supported in the literature, but is found in clinical practice
- these disorders have genetic/family implications, and speedy diagnosis of the index patient may allow for further characterisation of the family transmission and identification of individuals at greater risk of haemorrhage
- effective control of menorrhagia may avoid more drastic interventions that would otherwise be contemplated
- drugs that potentially potentiate the bleeding diathesis (aspirin, NSAIDs) should be avoided.

All patients should have a good history taken, with assessment at other bleeding sites. A good drug history, particularly response to aspirin is indicated. In women who have a history of excess bleeding at non-gynaecological sites, or in whom no other cause for menorrhagia is found, the following tests are indicated: FBC, PT (INR), aPTT, fibrinogen, TSH (hypothyroidism may cause acquired vWD), bleeding time (if available and with cognisance of poor sensitivity) and assays for vWD. Further tests of platelet function are usually only available at specialised centres.

Treatment of patients with menorrhagia may not be significantly different to that of patients with non-haematological-related bleeding, viz. the use of oestrogen-containing compounds and anti-fibrinolytics (such as tranexamic acid). However, DDAVP, for both haemophilia A carriers, mild type 1 vWD and some platelet disorders, may be a useful adjunctive agent in improving levels and/or function of the defective haemostatic component and ameliorating bleeding. For more serious bleeding, transfusions

of factor concentrates or platelets may be required – this should always be in consultation with an experienced physician or clinical haematologist. Aspirin and (often) NSAIDs should be avoided, and a Medic-Alert identification obtained. The genetic implications of the disorder should be reviewed with the patient, together with plans for future pregnancies if desired.

Thus, menorrhagia may be a seriously underrated and underinvestigated marker of an underlying bleeding diathesis, and each patient who presents with this symptom deserves to have this option considered in the diagnostic workup and therapeutic management.

## Management of chronic myeloid leukaemia

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The management of chronic myeloid leukaemia (CML) has undergone a remarkable transformation in the past decade from a malignancy for which cure was available to a minority (in the form of an allogeneic bone marrow (or peripheral blood stem cell) transplant), with the rest inevitably progressing to incurable blastic transformation and death, to a disease where control with a group of remarkably well-tolerated drugs is changing both the natural history of the disease, as well as turning previous therapeutic stratagems on their collective heads.

CML is a malignant proliferation of predominantly granulocytic lineage and is due to the presence of the Philadelphia chromosome, which is a *sine qua non* for the diagnosis. This represents a reciprocal translocation of genetic material from the long arm of chromosome 9 to chromosome 22 and *vice versa* – t(9;22)(q34;q11). This results

in partnering of two genes, namely *BCR* and *ABL* (which encode a tyrosine kinase involved in second messenger systems controlling growth and proliferation.) The resultant fusion protein, BCR-ABL represents an unregulated, permanently switched on tyrosine kinase responsible for phosphorylating tyrosine residues on a number of downstream proteins.

Previous non-transplant strategies at controlling the disease included:

- Hydroxyurea – a ribonuclear reductase inhibitor, which prevented proliferation and growth of all haematological progenitor cells, and controlled the white cell count.
- Interferon alpha (with or without the addition of low-dose chemotherapeutic agents such as cytosine arabinoside), which augmented the body's immune response against the tumour, as well as directly causing bone marrow suppression. This was more successful than hydroxyurea with longer overall survival rates; notably cytogenetic responses were observed that suggest-ed that the natural history of the disease was being modified.

However, in both cases, there was an almost inevitable progression after a number of years to accelerated and later blastic phase of the disease. The likelihood of progression depended on certain prognostic variables at presentation in patients with chronic stable phase (notably Sokal score) stage of disease and on the choice of therapy employed.

With the advent of targeted therapy, specific tyrosine kinase inhibitors have been developed against the *Abl* oncogene (as well as other tyrosine kinases). The first in this class was imatinib mesylate (Gleevec), which occupies the ATP binding site of the tyrosine kinase, and prevents subsequent phosphorylation of tyrosine residues on affected proteins. This drug was found to be active in patients resistant to, or intolerant of interferon therapy, and was proven to be effective in newly diagnosed CML in a seminal trial (the IRIS trial), which compared imatinib mesylate to interferon alpha with low-dose cytosine arabinoside. The new drug was so successful that most patients in the interferon arm subsequently crossed over to the trial drug arm. However, median survival has not been reached – at 3 years the overall survival of the patients receiving imatinib in IRIS was 92% (CI 90 - 95%) and freedom

**Imatinib mesylate is registered in South Africa, and is also available under a patient assistance programme for indigent patients – i.e. no patient in South Africa with CML should be denied access to this potentially lifesaving drug.**

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from transformation was 90%. This was significantly better than historical controls receiving interferon alpha plus low-dose cytosine arabinoside.

Moreover, with major and complete (absent Ph+) cytogenetic responses occurring at 93% and 87% at 36 months compared with 62% and 42% for patients receiving the interferon combination, it seems we are making a significant impact on the biology of the disease.

This drug is also able to produce 3 - 4 log reductions in molecular transcripts of BCR-ABL when assessed by quantitative reverse transcriptase polymerase chain reaction (RT-PCR). However, it is not able to produce a cure, as the CML stem cell remains resistant, and relapses rapidly occur when therapy is discontinued. Thus CML may be transformed into yet another chronic disease for which lifelong therapy is required. Side-effects may be

haematological (various cytopenias) or non-haematological (skin reactions, fluid retention, myalgias, bone pain, nausea and vomiting), but in general, the drug is well tolerated. Imatinib mesylate is registered in South Africa, and is also available under a patient assistance programme for indigent patients – i.e. no patient in South Africa with CML should be denied access to this potentially lifesaving drug.

Drug resistance remains the major, although uncommon, finding especially if imatinib is started early in the disease course. This may be mediated through various mechanisms – some of which may be abrogated by increasing the dose from the standard 400 mg (in chronic stable phase) to 600 mg / 800 mg daily. It behoves the practitioner to monitor the cytogenetic status of the disease with regular bone marrow examinations.

If resistance is encountered, further drugs are either in clinical development, or have been registered elsewhere and are awaiting registration in South Africa (notably dasatinib registered as Sprycell in the USA, and nilotinib). These drugs are more potent and investigations into first-line use are underway. For patients who have a bone marrow transplant option, failure to respond to a tyrosine kinase inhibitor is now the major indication to proceed with this modality of therapy.

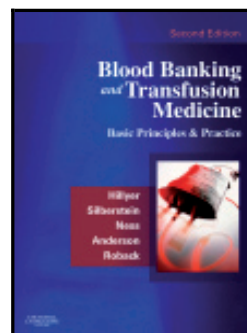
The management of CML has now reached the stage where, although problems may still occur, most patients are now well controlled on drugs with minimal side-effects and can look forward to a longer survival with a good quality of life.

## Blood Banking and Transfusion Medicine, 2nd edition Basic Principles and Practice

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