Introduction

The mainstay of haemophilia care remains replacement of the missing clotting factor; FVIII in the case of haemophilia A and FIX for haemophilia B. Regular replacement therapy is used to prevent bleeds, whereas episodic replacement therapy ensures rapid homeostasis and optimal treatment of bleeds. The most serious complication related to haemophilia treatment is the development of alloantibodies (or inhibitors) to FVIII or FIX, which neutralise the coagulant activity of clotting factor concentrate and thereby render standard replacement therapy ineffective. Inhibitors increase the risk of uncontrollable bleeding, increased morbidity and mortality, orthopaedic complications and disability, reduced quality of life and increased health care costs.1-3,5

This Haemophilia Masterclass, hosted by Novo Nordisk, reviewed the treatment of haemophilia with inhibitors in resource-constrained settings in South Africa and South America. Dr Johan Potgieter considered variances in inhibitor treatment strategies and management in the South African context, Professor Margareth Ozelo presented her experiences from Brazil in individualising on-demand dosing with rFVIIa under current economic challenges and Professor Johnny Mahlangu raised the question of standardising treatment protocols for inhibitor patients.

KEY MESSAGES

- Inhibitors may develop in 10-15% of haemophilia A patients and in 1-3% of haemophilia B patients
- Primary treatment goals for haemophilia with inhibitors are control of haemostasis and permanent inhibitor eradication
- Haemophilia with inhibitor must be managed in consultation with a haemophilia treatment centre (HTC)
- High-responders with inhibitor titres >5BU will not achieve homeostasis with increased clotting factor infusion
- The bypassing agents rFVIIa and APCC are used for bleeding control in high-responder patients with either high or low inhibitor titre levels
- Critical to haemostatic efficacy are individual response to therapeutic agent, type of bleed and time between start of bleed and treatment with adequate dose
- Early treatment of bleeds is associated with better overall outcomes
- rFVIIa is well-suited for use in the home treatment setting
- Successful inhibitor eradication is achieved in approximately 70% of those submitting to Immune Tolerance Induction (ITI)
- Few guidelines make specific recommendations for bleeding control in inhibitor patients
- The South African Haemophilia Foundation treatment guidelines for haemophilia in South Africa offer limited advice on management of different bleed types in haemophilia with inhibitors
Inhibitors: A brief overview

Inhibitors may develop in 10-15% of haemophilia A patients and in 1-3% of haemophilia B patients.6,7,20 The life time risk of inhibitor development in haemophilia A is 5-10% in mild or moderate disease and 20-30% in severe disease.8,24,31 Age-adjusted analysis of UK data indicates a bimodal risk of inhibitor development, with higher incidence in those younger than 5 years or older than 60 years.4,9,10 It is postulated that increased incidence in older patients may be due to increased surgical procedures and intensive treatments, as well as declining immune regulation. Circumstances indicating the need to check for inhibitor development are described in Table 1.

**Table 1. When to check for inhibitors**11,12

<table>
<thead>
<tr>
<th>Circumstances</th>
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<tbody>
<tr>
<td>Family history of inhibitors</td>
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<td>Before elective invasive procedures</td>
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<tr>
<td>Suboptimal clinical or laboratory response to concentrate</td>
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<td>Before and after a switch of concentrate</td>
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<td>2-4 weeks after intensive treatment of 5 exposure days (EDs) or surgery in mild or moderately affected patients</td>
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<tr>
<td>Every 3rd or 5th ED or every 3 months if concentrate exposure has occurred until 20 EDs, then every 10 EDs between 21 and 50 EDs, then 3-6 monthly until 150 EDs</td>
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<td>Once or twice a year indefinitely.</td>
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**Classification of inhibitors**

Bethesda units (BU) are a measure of coagulation factor inhibitory activity in plasma. A titre of 1BU/ml implies a level of inhibitor sufficient to neutralise 50% of the clotting factor in 1ml of plasma.13,24 The anamnestic response may be high (>5BU/ml) and homeostasis will not be achieved with increased FVIII infusion, as inhibitor titres increase rapidly upon antigen exposure. Inhibitor titres of low-responders (≤5BU/ml) do not increase with antigen exposure and factor replacement therapy can be continued.13 A transient response may also occur, although the acute increase in inhibitor titre is not sustained and factor replacement therapy can be continued (Figure 1).13

**Inhibitors: Classification**

- **Titer**: (1 BU/mL = neutralizing Ab of 50% FVIII or FIX in 1mL of plasma)
  - High: > 5 BU/ml
  - Low: ≤ 5 BU/mL
- **Anamnestic response**:

<table>
<thead>
<tr>
<th>BU 100</th>
<th>Time</th>
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*High responder*

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*Low responder*

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*Transient*

**Figure 1. Variation of anamnestic response in haemophilia with inhibitors**
Bypassing Agents

Bypassing agents are used for bleeding control in high-responder patients with either high or low inhibitor titre levels.\textsuperscript{20,21} These agents are activated prothrombin complex concentrate (APCC) and recombinant activated factor VII concentrate (rFVIIa) (Table 2). The therapeutic response to bypassing agents is unpredictable with inter- and intra-individual variability; and no laboratory assay is validated to monitor the efficacy and safety of treatment.\textsuperscript{28} Efficacy of bleeding control is similar for the two agents with approximately 80\% resolution of all bleeds.\textsuperscript{14,16-22}

<table>
<thead>
<tr>
<th>Table 2. Characteristics of bypassing agents used in haemophilia A and B with inhibitors\textsuperscript{23,24}</th>
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<tbody>
<tr>
<td><strong>Bypassing agent</strong></td>
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<tr>
<td><strong>Therapeutic indication</strong></td>
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<td><strong>Recommended regimen(s)</strong></td>
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<td><strong>Source</strong></td>
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<td><strong>Storage requirements</strong></td>
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<tr>
<td><strong>Diluent volume</strong></td>
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<td><strong>Duration of administration</strong></td>
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<td><strong>Plasma half-life</strong></td>
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<td><strong>Inhibitor anamnesis</strong></td>
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<td><strong>Association with antifibrinolytic agents</strong></td>
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Inhibitor treatment options

Primary treatment goals for patients with inhibitors are control of haemostasis and permanent eradication of the inhibitor by inducing tolerance, in order to return to factor replacement therapy.\textsuperscript{2,3,6,9,28,29}

Guidelines for bleeding control

Critical factors for haemostatic efficacy include individual response to therapeutic agent, the type of bleed and the time between start of bleed and treatment with adequate dose. Few of the available guidelines make recommendations for the management of specific bleed types. United Kingdom Haemophilia Centres Doctors Organisation (UKHCDO) guidelines for the treatment of specific bleeding problems are summarised in Table 3; with the recommendation that arrangements should be made to treat bleeds within 2 hours at home or hospital. The South
African Haemophilia Foundation Medical and Scientific Advisory Council (SAHF MASAC) treatment guidelines (Table 4) offer limited advice for factor VIII or IX inhibitor management options. It is generally accepted that inhibitor patients must be managed in consultation with a HTC that is experienced in the treatment of inhibitors. Tranexamic acid is to be considered in all patients not receiving high doses of APCC, especially for mucosal bleeds. Dr Potgieter noted that tranexamic acid can only be used with high doses of APCC if the agents are administered at least 6 hours apart and patients should be closely monitored for thrombo-embolic phenomena. Patients receiving bypassing agents, particularly adults with associated co-morbidities, are at risk of thrombosis and should be clinically monitored on a regular basis for such events.

Low-responding haemophilia with inhibitor may be treated with specific factor replacement at a much higher dose, to stop bleeding by neutralising the inhibitor with excess factor activity. It is preferable to increase the frequency of FVIII/FIX infusions rather than increasing the administered concentration. Those with a history of high-responding inhibitor, but with low titres, may be treated similarly in an emergency until an anamnestic response occurs. This can usually be expected within the first 3 days of exposure. Patients with mild or moderate haemophilia A with high inhibitor prevalence mutations or a family history of inhibitor, should be treated with DDAVP wherever possible to avoid FVIII exposure.

With an inhibitor level of >5BU, it is unlikely that specific factor replacement will be effective and alternative agents such as rFVIIa and APCC are used.

### Table 3. UKHCDO guidelines: Treatment of specific bleeding problems in haemophilia with inhibitor

<table>
<thead>
<tr>
<th>Soft tissue bleeds</th>
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<tr>
<td>• rFVIIa 90μg/kg 2-3 hourly; assess after each dose</td>
</tr>
<tr>
<td>• APCC 50-100U/kg; review after 8h</td>
</tr>
<tr>
<td>If partial response after 3 doses rFVIIa or 8h after APCC, continue with same; reassess after 24h or increase dose/frequency of treatment</td>
</tr>
<tr>
<td>If no response or bleed worsens, switch to alternate bypassing agent</td>
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<tr>
<td>Continue until full recovery of muscle function; taper dose and frequency</td>
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<table>
<thead>
<tr>
<th>Joint bleed</th>
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<tr>
<td>• Immobilise affected joint and use ice packs</td>
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<tr>
<td>• Uncomplicated haemarthroses are treated the same as soft tissue bleeds</td>
</tr>
<tr>
<td>• Continue until full joint recovery; taper dose and frequency with improvement to the joint</td>
</tr>
<tr>
<td>• Early haemarthroses may be treated with a single dose of rFVIIa 270μg/kg; assess after 4-6h</td>
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<th>Intracerebral bleed</th>
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<tr>
<td>• If inhibitor titres are low, FVIII/FIX concentrate should be considered with regular monitoring; switch to a bypassing agent if the inhibitor titre rises</td>
</tr>
<tr>
<td>• rFVIIa 90-120μg/kg every 2h; assess response after 2 treatments</td>
</tr>
<tr>
<td>• APCC 100U/kg; assess after 4h</td>
</tr>
<tr>
<td>If partial response, increase dose or frequency</td>
</tr>
<tr>
<td>If no response or deterioration, switch to an alternative agent</td>
</tr>
<tr>
<td>If inadequate response to alternate agents, sequential treatment with these products can be considered</td>
</tr>
<tr>
<td>• Intensive treatment to be continued for at least 5 days with regular radiological assessment</td>
</tr>
<tr>
<td>• Taper dose or frequency as improvement occurs</td>
</tr>
<tr>
<td>• Prophylactic treatment with rFVIIa or APCC to be started upon resolution of the intracerebral bleed and continued for at least 6 months</td>
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</table>
Sequential or combined therapy is to be considered for life or limb-threatening bleeding that is unresponsive to treatment with either bypassing agent alone. Variables influencing choice of bypassing agent are listed in Table 5. Plasma-derived APCC (comprised of vitamin K dependent factor partially activated II, VII, IX and X) may contain trace amounts of FVIII and an anamnestic response may occur with use in haemophilia A (30%). Professor Ozelo cautioned that APCC is not recommended for use in haemophilia B with anaphylactic response and that patients who have experienced allergic reactions to FIX should be treated with rFVIIa. She recommends that FIX replacement therapy take place in the clinic setting, particularly if there is a family history of anaphylaxis or inhibitors, because it is not possible to predict if the patient will have an anaphylactic response.

Professor Mahlangu described the range of rFVIIa dosing protocols used in real world treatment settings (≤90μg/kg to ≥270μg/kg), with a trend to using higher doses for single administration and lower doses for multiple infusions.

### Table 4. SAHF MASAC guidelines: Factor VIII or IX inhibitor management options

**Haemophilia A with inhibitors - acute bleeding episodes**

- Ice/cold pack – 5 minutes on, 10 minutes off
- Immobilise joint with a splint

**Low Responder (<5BU)**
- Five Factor VIII at 2-3 times the normal dose
- Monitor response clinically
- Frequent factor recovery levels

**High Responder (>5BU)**
- APCC 50-100U/kg q12-24h for 3 days or until clinical improvement
  - Infuse at 2IU/kg/min
  - Do not exceed single dose of 200IU/kg
  - Do not use antifibrinolytic drugs (e.g. tranexamic acid) concurrently because of the risk of thromboembolism
- rFVIIa 90μg/kg 2-3h or by continuous infusion (at 20μg/kg/h) until clinical improvement
  - New single dose of 270μg/kg may be used
  - Tranexamic acid 15-25mg/kg/dose po/IV q6-8h may be used concurrently with rFVIIa

**Haemophilia A with inhibitor - long-term management: Immune tolerance (IT)**

- IT should be initiated at a HTC
- Successful therapy (eliminating the inhibitor) may take months
- Several regimens are effective – the Dutch regime (25IU/kg Factor VIII 3 times per week) is the most affordable

**Haemophilia B with inhibitor**

- APCC should be carefully monitored for anaphylaxis and anamnestic reaction. Therefore patients are best treated with rFVIIa, the only bypassing agent that does not contain FIX
- rFVIIa 90-120μg/kg IV every 2-3 hours as bolus or 20μg/kg/hour as continuous infusion. Single dose of 270μg/kg may be used
  - Antifibrinolytic can be given concurrently with rFVIIa
- There is no evidence to guide tolerisation procedures in patients with haemophilia B and inhibitors. Plasma-derived FIX may be used for tolerisation with careful monitoring of anaphylactic reactions

### Table 5. Variables influencing choice of bypassing agent

- Age of patient
- Venous access
- Historical response to treatment
- The site and nature of the bleed
- Inhibitor status and titre
- Availability
- Cost
Immune Tolerance Induction (ITI) – Eradicating inhibitors

The rationale underpinning ITI for inhibitor management is that continuous exposure to the relevant clotting factor for long periods can lead to the disappearance of neutralising alloantibodies. Successful inhibitor eradication is obtained in approximately 70% of those submitting to ITI, thereby restoring efficacy of replacement therapy. The Dutch protocol for ITI recommends 25IU/kg FVIII every other day, with success rates of 61-88% over a period of 1-12 months.

Professor Ozelo noted that the Dutch protocol is the most cost-effective and works quite well. From the Brazilian Ministry of Health, retrospective analysis of severe haemophilia A patients with high-responding inhibitors ≥18 years of age who underwent ITI and were using bypass agents before ITI shows a significant reduction in annualised bleeding rate and annualised joint bleeding rate. Furthermore, median costs of factor concentrate is lower at 11 months of ITI than in the year preceding ITI. Spend on factor concentrate continued to decrease with each successive year after immune tolerance was attained, as homeostasis is achieved more rapidly and there is a decreased incidence of anamnesis.

Benefits of early bleed treatment in inhibitor patients

Bleeding into the joints has the immediate consequences of pain, swelling and loss of mobility; and with repeated bleeds over time, blood in the joints leads to structural and inflammatory changes. Professor Mahlangu noted that patients usually recognise early symptoms of bleeding, described as a tingling sensation or ‘aura’, even before the manifestation of any physical signs. By acting on this intuition, home treatment avoids delays in treatment and is associated with better overall outcomes independently of hospital treatments.

Early treatment (<2 hours) leads to faster bleeding resolution, minimises the risk of re-bleeding and improves sustained bleeding control. Other benefits of prompt management include a likely delay of arthropathic progression and disability; the use of less product (more cost-effective) and a delay or prevention of the need for more expensive interventions later.

Professor Ozelo commented on the success of home treatment in Brazil, which has been the single best improvement to their haemophilia care programme servicing 12,000 patients. Every patient, regardless of geographical location, is assured to have at least a single dose accessible for early treatment.

rFVIIa in home treatment

Professor Ozelo and Dr Potgieter considered both trial and haemophilia registry data supporting the efficacy and tolerance of rFVIIa implementation in the home treatment setting. A review of 8,758 bleeding episodes in 793 patients with varied rFVIIa dosing (90-270µg/kg, 1-3 doses) showed efficacy of 81%-96% with only 3 thrombotic events. Early treatment with rFVIIa allows for homeostasis to be attained using relatively low doses, effectively using half the dose required to achieve homeostasis in late treatment. Earlier initiation of treatment with rFVIIa is also associated with a reduced risk of re-bleeding into the same joint (4-5% after 24 hours with early treatment, 13-14% after 24 hours with late treatment). Improved short-term outcomes for inhibitor patients treated with rFVIIa include rapid pain relief, early mobilisation, reduced need for hospital visits and return to daily life sooner. Dr Potgieter noted that rFVIIa is well suited for home use. It is stable at room temperature (<25°C) and does not require refrigeration. After reconstitution, it is stable for 6 hours at 25°C and 24 hours at 2-8°C. Furthermore, the low volume of rFVIIa injection means it can be administered rapidly over a period of 2-5 minutes.
Challenges of home treatment

Challenges to home-based treatment include accessibility of treatment product, venous access and home therapy training and proficiency. Resistance on the part of the child is also a common challenge. Parental issues include squeamishness about giving an injection and a lack of confidence in their ability to do so, fearing that they will do something wrong or cause pain. Uncertainty about which treatment to use and anxiety about potential side effects and contaminated blood products, as well as “being responsible” for a treatment that has harmed their child, are confounding factors in the home treatment setting. The balance between the desire for a normal active lifestyle and protecting the child from risk is also difficult.52

Improving home treatment

Professor Mahlangu considered the means by which to improve adherence to home treatment. He suggests that an implanted venous access device can make administering injections much easier and may be required when administering prophylaxis in younger children. An understanding of and belief in the necessity of treatment and a good relationship with the health care providers are strong motivators for adherence. Experience of symptoms encourages adherence to treatment, but paradoxically, the lack of symptoms after a period of prophylaxis may prove a barrier to adherence.53

What is the current situation in South Africa?

In 2015, the South African national registry recorded 2216 people with haemophilia (A=1858, B=358). Considering a population of 55 million, it is suspected that less than half of South Africans with haemophilia are known to the registry. While some diagnosed patients may not be registered; Dr Potgieter also suspects underdiagnosis of predominantly mild to moderate disease. Registry data from 2017 reflects 181 inhibitor patients (A=168, B=13) compared to 135 inhibitor patients in 2007.54 However, 65% of known inhibitor patients are accounted for by the KwaZulu-Natal and Gauteng provinces only (Figure 2), implying missed diagnosis of inhibitor development in some areas.

![Figure 2. Provincial distribution of haemophilia with inhibitors: South Africa 2015](image-url)
The South African Department of Health supports the National Haemophilia Program, providing haemophilia care through a network of HTCs staffed by multidisciplinary health care professionals and haemophilia nurse coordinators. Home therapy is standard of care for uncomplicated haemophilia and >75% of eligible severe patients have been trained for home therapy. All current haemophilia medications, apart from desmopressin, have been included in the Essential Drugs List at hospital level. Available modalities to control haemostasis are replacement therapy (FVIII/FIX concentrates), bypassing agents (rFVIIa and APCC), antifibrinolytic agents (tranexamic acid), adjunctive agent (fibrin glue) and RICE (rest, ice, compression, elevation).

**Treating haemophilia A with high-responder inhibitors - The current South African approach**

Home therapy with bypassing agents is available to all patients on private medical schemes, but only some public sector patients have access to a stat dose for home therapy (rural) and rely on access to bypassing agents through local clinics. Barriers to home therapy are predominantly cost, hospital approval and lack of expertise in peripheral regions, often with no dedicated haemophilia nurse to monitor therapy. Many patients are reluctant to self-infuse.

In South Africa, choice of bypassing agent varies between HTCs, influenced by availability and which agent will be the first to expire. Circumstances in which rFVIIa is favoured are allergic reaction to FIX and if ITI is considered as a future treatment option in the case of anamnesis. For major bleeds, APCC is preferred due to its longer half-life and it is also perceived to be cheaper. APCC is favoured for late presentation bleeds. Most paediatricians prefer APCC for older patients and rFVIIa for younger patients.

Managing mild to moderate bleeding is variable between HTCs. Most prefer outpatient treatment, although paediatric centres and those dependent on access to hospital (rural) will admit. Some centres do not treat the bleed, using only RICE and analgesics. If previous inhibitor titre <5BU, high dose FVIII is used. Doses used for bypassing agents range between HTCs.

**Paediatric:** rFVIIa 90-270μg/kg stat with variable reassessment time; APCC 50-75U/kg 12 hourly or daily.

**Adult:** rFVIIa 90μg/kg 3 hourly or 270μg/kg stat (some daily); APCC 50-100U/kg (sometimes 60-80U/kg) 6-12 hourly.

Managing severe bleeding episodes (e.g. limb or life threatening). All HTCs admit and use bypassing agents (variable regimens) and tranexamic acid.

**Paediatric:** rFVIIa 270μg/kg stat then 90μg/kg 2-4 hourly; APCC 75-100U/kg 12 hourly or 50-100U/kg 8 hourly.

**Adult:** rFVIIa 90μg/kg 3 hourly (or more frequently) or 270μg/kg stat (some daily); APCC 75-100U/kg 6-8/12 hourly.

**How to improve standard of care in South Africa**

Dr Potgieter and Professor Mahlangu discussed a range of factors that will enable improvement of haemophilia care, particularly in patients with inhibitors. Core resources required for comprehensive care include access to therapy, haematologists, haemophilia nurses, musculoskeletal experts, laboratory specialists, psychologists and social experts. Education measures to improve awareness amongst health care workers should minimise the risk of inhibitor development. The principle of early/home treatment needs to be promoted through patient education; and mobilisation of patients will improve accessibility of care.

ITI should be provided as standard of care to all children. Updated and standardised protocol for management of different types of acute bleeding (non-target joint, joint, non-joint, intracranial and mucous membrane), inclusive of definitions and suitable assessment of response, will enable treatment optimisation. There should however, still be scope for individualised treatment decisions based on the characteristics of the patient and specific morbidity. Bypassing agents need to be made available at regional hospitals where suitably qualified clinicians can liaise with a HTC.
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