sciendo

CASE STUDY

A creative approach to managing a case of haemophilia A with inhibitors in a low-resource country: case report

Simran Bhatia, Archana M V, Vasudeva Bhat, Ganesh M Balthillya, Sulochana Badagabettu

The development of antibodies to therapeutic factor VIII, known as inhibitors, is a leading cause of morbidity and mortality in people with haemophilia. This is particularly challenging in areas where access to novel treatment options is limited. This case report presents a clinical scenario in South Western India involving a 16-year-old male with severe haemophilia A with high titre inhibitors, who sustained a tibia-fibula shaft fracture necessitating emergency surgical intervention. The successful management of this patient required a multidisciplinary approach, encompassing haemostasis optimisation, innovative factor replacement strategies to work around financial constraints, and a comprehensive rehabilitation plan. The patient's history of multiple factor VIII concentrate transfusions contributed to inhibitor development. Limited funds for bypassing agents prompted the utilisation of fresh frozen plasma to achieve haemostasis before access to FEIBA and recombinant factor VII. Emicizumab, a subcutaneously administered bispecific antibody, was used to assist perioperative haemostasis. A comprehensive rehabilitation plan with regular physiotherapy was followed. Emicizumab prophylaxis was initiated and the patient now shows improvement. This case emphasises the importance of novel treatment options such as FEIBA and emicizumab in dealing with complications in haemophilia such as inhibitors. In

©Shutterstock/luchschenF

A case study from South Western India emphasises the importance of novel treatment options in cases of haemophilia with inihibitors in the context of a need for surgery

SIMRAN BHATIA
Kasturba Medical College, Manipal Academy of Higher Education, Manipal, India. Email: simranbhatia99@gmail.com

ARCHANA M V
Division of Pediatric Hematology and Oncology, Kasturba Medical College, Manipal Academy of Higher Education, Manipal, India. Email: archana.mv@manipal.edu

VASUDEVA BHAT
Division of Pediatric Hematology and Oncology, Kasturba Medical College, Manipal Academy of Higher Education, Manipal, India. Email: vasudev.bhat@manipal.edu

GANESH M BALTHILLYA
Department of Physiotherapy, Manipal College of Health Professions, Manipal Academy of Higher Education, Manipal, India. Email: ganesh.bm@manipal.edu

SULOCHANA BADAGABETTU
Department of Fundamentals of Nursing, Manipal College of Nursing, Manipal Academy of Higher Education, Manipal, India. Email: sulochana.k@manipal.edu

resource-limited settings, there is still a need to improve the availability of these life-saving interventions to optimise surgical outcomes in such cases.

Keywords: *Haemophilia A, Inhibitors, Emicizumab, FEIBA, Surgical procedure, Case report*

Haemophilia A is a rare bleeding disorder caused by inadequate levels of clotting factor VIII (FVIII) [1]. Standard of care for severe haemophilia A requires prophylactic therapy, which involves routine infusions of FVIII concentrates to help prevent bleeding episodes and chronic joint damage. The emergence of neutralising antibodies to therapeutic FVIII, known as inhibitors, is a significant complication associated with the treatment of haemophilia A [2]. These antibodies can hinder the effectiveness of replacement therapy and result in increased costs associated with treatment [3]. Inhibitors typically arise within the initial 50 exposure days but can also be a concern for older patients [4].

Globally, the incidence of inhibitors in haemophilia A cases is estimated to be around 33% [3]. In India, the prevalence of inhibitors varies in different regions, with one study noting incidences ranging from 5.2% in Mumbai to 21% in Chennai [1]. The Indian Academy of Pediatrics recommends the use of bypassing agents for the treatment of bleeds in people with haemophilia with inhibitors [5], but their high cost precludes routine use. Immune tolerance induction (ITI) is also recommended for the eradication of inhibitors, but again, the high cost involved is a major challenge for widespread use [5]. The use of emicizumab is limited but studies show promising results in Indian children [6].

In people with haemophilia (PwH) who have inhibitors, surgery poses additional challenges and considerations. The advent of bypassing agents represents a crucial advancement; however, despite the benefits of using these agents to maintain haemostasis during major surgeries [7], it is essential to recognise that this comes with a significant economic impact, affecting access in low-resource settings. Here, we present a creative approach to managing a person with haemophilia A (PwHA) with inhibitors in a low-resource country who needed emergency surgical treatment.

CASE PRESENTATION

A 16-year-old male with severe haemophilia A (FVIII <1%) and known to have inhibitors presented to the Emergency Department at our hospital with complaints of severe pain and inability to move his right leg following a slip and fall from stairs at his home on 17/10/2021. He was diagnosed with haemophilia A in 2006 at the age of two years with a history of bleeding symptoms. There was no known family history of haemophilia, however his younger brother was also diagnosed with haemophilia A. He had a history of multiple hospital admissions and complications including recurrent bilateral knee haemarthrosis, intracranial haemorrhage (08/09/2013), haematuria (06/05/2013), and intra-abdominal haematoma (14/08/2013). He was managed with on-demand clotting factor concentrates with plasma-derived and recombinant FVIII infusion following each episode of

Figure 1. X-rays of right leg (A/P) lateral view, showing closed tibia-fibula (transverse) shaft fracture (left) and interlocking nail post-surgery (right)

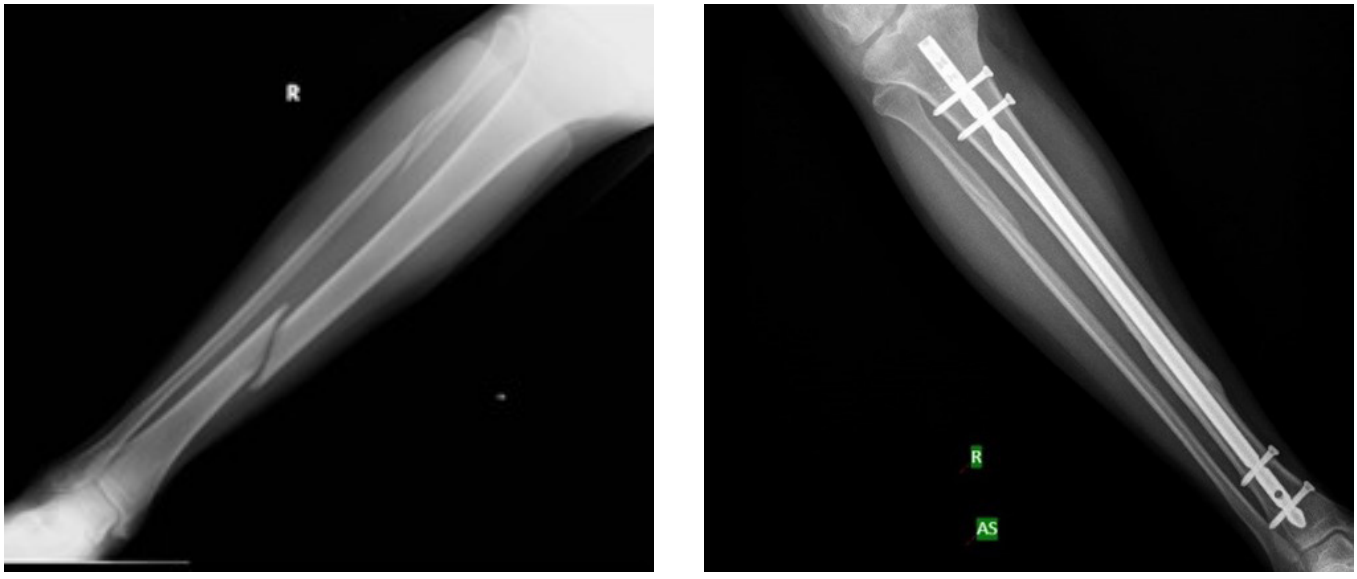
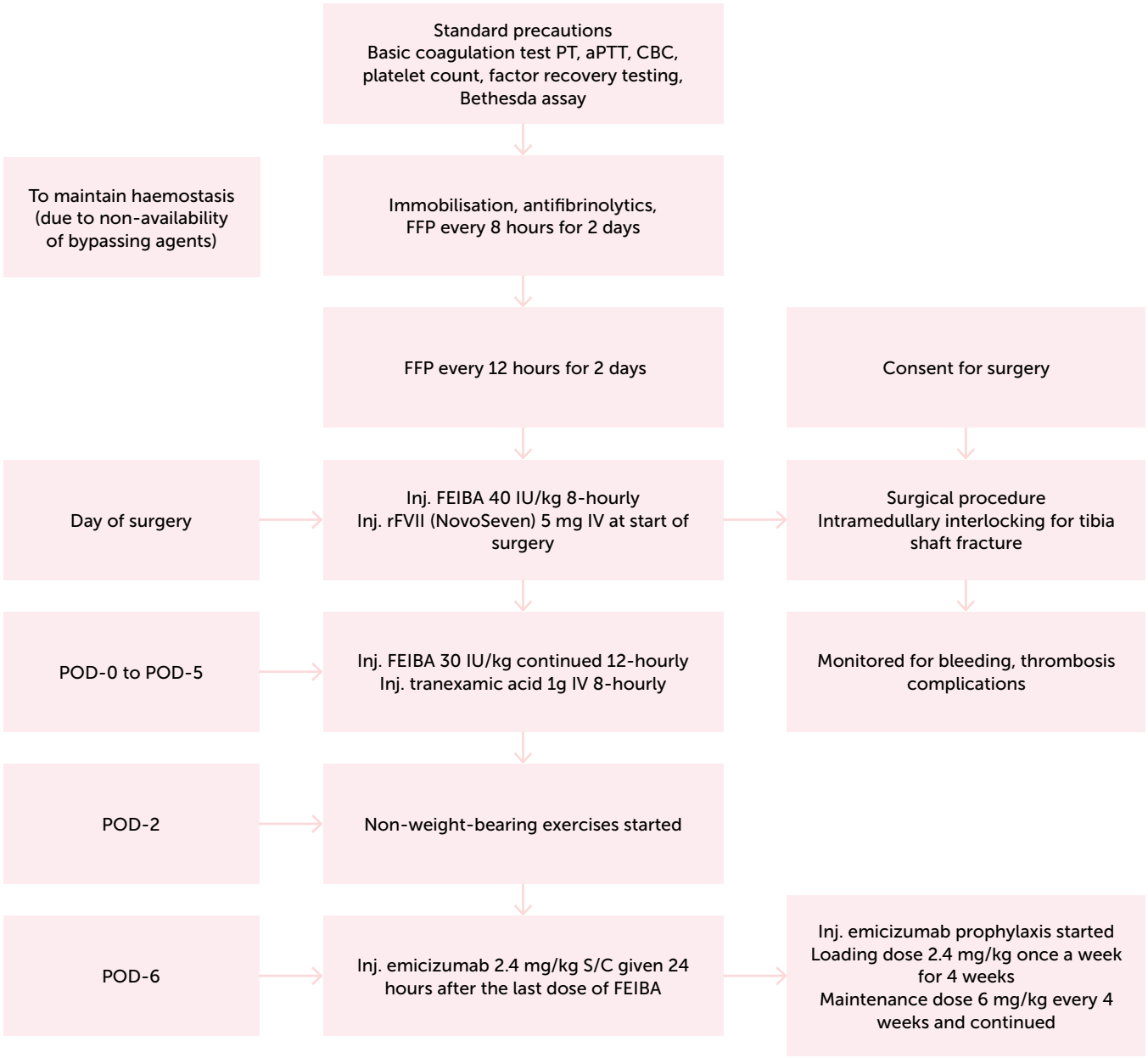


Figure 2. Plan of action for management of perioperative haemostasis



PT: Prothrombin time aPTT: Activated partial thromboplastin time CBC: Complete blood count FFP: Fresh frozen plasma
POD: Postoperative day

bleeding manifestation, and was on regular six-monthly follow-up on an outpatient basis with annual inhibitor screening. In 2018, during routine inhibitor screening, he was found to be inhibitor-positive with 2.1 Bethesda units (BU). Multiple hospital admissions at a young age requiring intensive treatment with FVIII infusions would have predisposed him to develop an inhibitor.

On examination, he was found to have diffuse swelling and tenderness over the shin and significant compromise in mobility suggestive of right tibia/fibula fracture. He was also noted to have chronic swelling and decreased mobility of bilateral knee joints suggestive of chronic synovitis. His right lower limb was immobilised with a slab and his leg was closely monitored for any sign of compartment syndrome. X-ray of the right leg (AP/lateral view) showed a closed tibia-fibula (transverse) shaft fracture (Figure.1).

Surgery for an intramedullary interlocking nail for the tibia shaft fracture was planned; however, factor recovery was found to be inadequate and repeat inhibitor assay (modified Bethesda assay) showed a high titre inhibitor at 126BU. Therefore, careful management

was required to achieve adequate haemostasis before and after surgery. A treatment plan was developed for management to achieve perioperative haemostasis (Figure 2).

The weight of the patient was 75kg. Due to constraints posed by his financial situation and due to FEIBA or recombinant factors not being readily available, he was given 3 units of fresh frozen plasma (FFP) every eight hours for two days, then every 12 hours for two days to maintain haemostasis until FEIBA could be arranged. He was scheduled for an intramedullary interlocking nail for tibia shaft fracture on 23/10/21, six days after his fall. On the day of surgery, FEIBA (factor VIII bypassing agent) 40 IU/kg was administered every eight hours and a single dose of recombinant factor VII (rFVII; NovoSeven) 5 mg (66 µg/kg) IV slow push at the time of surgery.

From postoperative day (POD) 0 to POD-5, the patient was given FEIBA 30 IU/kg IV every 12 hours and tranexamic acid 1g IV every eight hours. He was carefully observed for signs of bleeding and thrombosis. Twenty-four hours post the last dose of FEIBA, emicizumab 180mg (2.4 mg/kg) was given subcutaneously to maintain haemostasis, as it is effective despite the presence of inhibitors.

To optimise the patient's recovery, we implemented a comprehensive rehabilitation plan. Initially, we applied a foot drop splint to the right foot, ensuring a neutral position for proper healing. Concurrently, sensory re-education training commenced in the first week after the injury to enhance sensory function and improve foot awareness. During the second week, shortly after the surgery on POD-2, the patient began using a walker for standing and walking, with no weight placed on the right foot. As progress was made, by POD-6, the patient advanced to partial weight-bearing while standing and walking with the walker. This step-by-step method facilitated muscle strengthening and coordination, fostering improved foot functionality. At the eight-week follow-up, the patient showed improved muscle strength and functional ability in the affected limb. He was able to progress to full weight bearing and is now fully rehabilitated.

The patient was followed up on an outpatient basis two weeks after surgery, then regularly for eight weeks. During this time, he reported no acute bleeding in the affected limb or from the incision site. Haemophilia Joint Health Scores (HJHS) from the presurgical to post-surgical period are shown in Figures 3 and 4. The patient continued to receive emicizumab prophylaxis every four weeks to facilitate healing. For the first four weeks, a loading dosage of 2.4 mg/kg was delivered once a week via subcutaneous injection; from the fifth week onwards a maintenance dose of 6 mg/kg was administered every four weeks. The four-weekly prophylactic regimen takes into account the cost and long process of availing emicizumab; the patient attends the hospital as an outpatient to receive his prophylaxis. It is currently planned that he will receive life-long emicizumab prophylaxis due to the presence of high-titre inhibitor, inability to initiate ITI (due to its a high cost and time-intensive nature), and history of frequent bleeds and hospitalisations.

No post-surgical bleed was reported at six-month and one-year follow-up. The wound was well approximated and healed with time. The patient has had no breakthrough bleeds and his HJHS score shows improvement with emicizumab prophylaxis.

A timeline giving an overview of the patient's history and this episode of care is showin in Figure 5.

DISCUSSION

One of the major challenges in the treatment of haemophilia A is the emergence of antibodies, or inhibitors, that can negate the efficacy of replacement therapy by neutralising the replaced factor VIII [1]. This complication affects around 33% of PwHA globally and can have serious consequences [3]. Epidemiological studies have measured the burden of inhibitor-positive haemophilia in India, with results varying between different states and regions. Ghosh et al. report the overall prevalence of inhibitors in India as 8.2% [8]. A study by Pinto et al. compared the prevalence of inhibitors in different regions in India, reporting Mumbai as having the lowest incidence at 5.2%, and Chennai the highest with 21% [1]. Other studies note inhibitor incidences in North-East India as 3.5% [9] and Western India as 20.57% [10].

Inhibitor development is multifactorial, with risk factors including disease severity, early exposure to FVIII concentrates, and genetic factors. Inhibitors arise most frequently in severely affected patients on treatment from a young age [11]. Our patient was diagnosed with haemophilia A at the age of two years and underwent multiple FVIII concentrate transfusions during childhood, putting him at high risk for the development of inhibitors.

Definitive diagnosis of inhibitors is made by quantifying the inhibitors through Bethesda assay or Nijmegen Modified Bethesda assay. One Bethesda unit (BU) is defined as the amount of inhibitor that results in 50% residual FVIII activity [12]. Based on inhibitor titre, patients are classified as low (<5 BU) or high (>5 BU) responders; management depends on whether the

Figure 3. Haemophilia Joint Health Score (HJHS) for right knee and right ankle

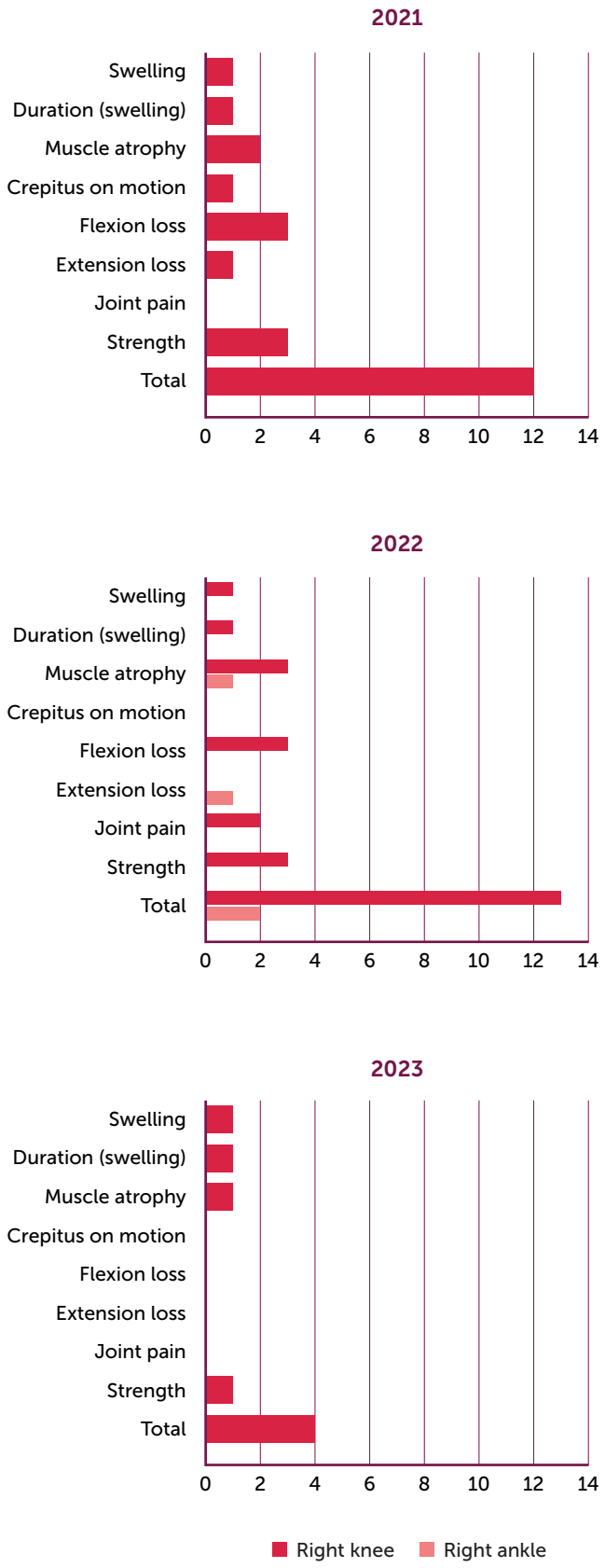
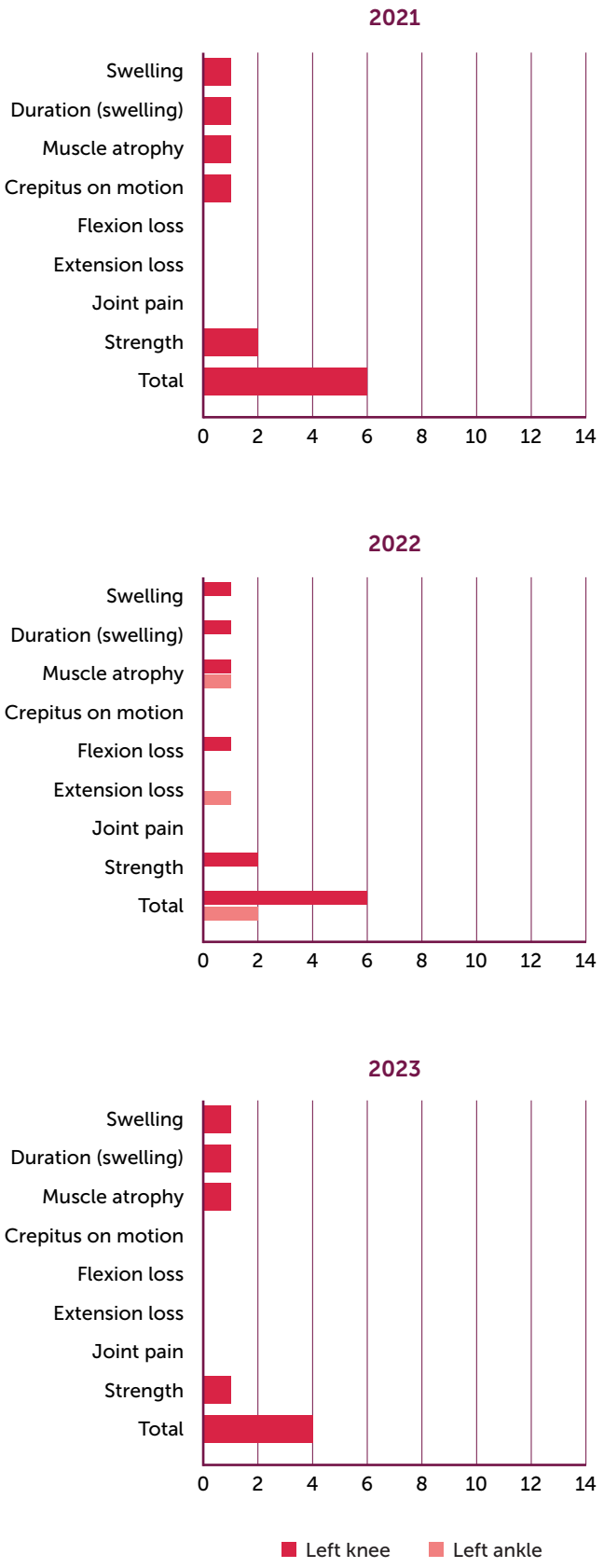
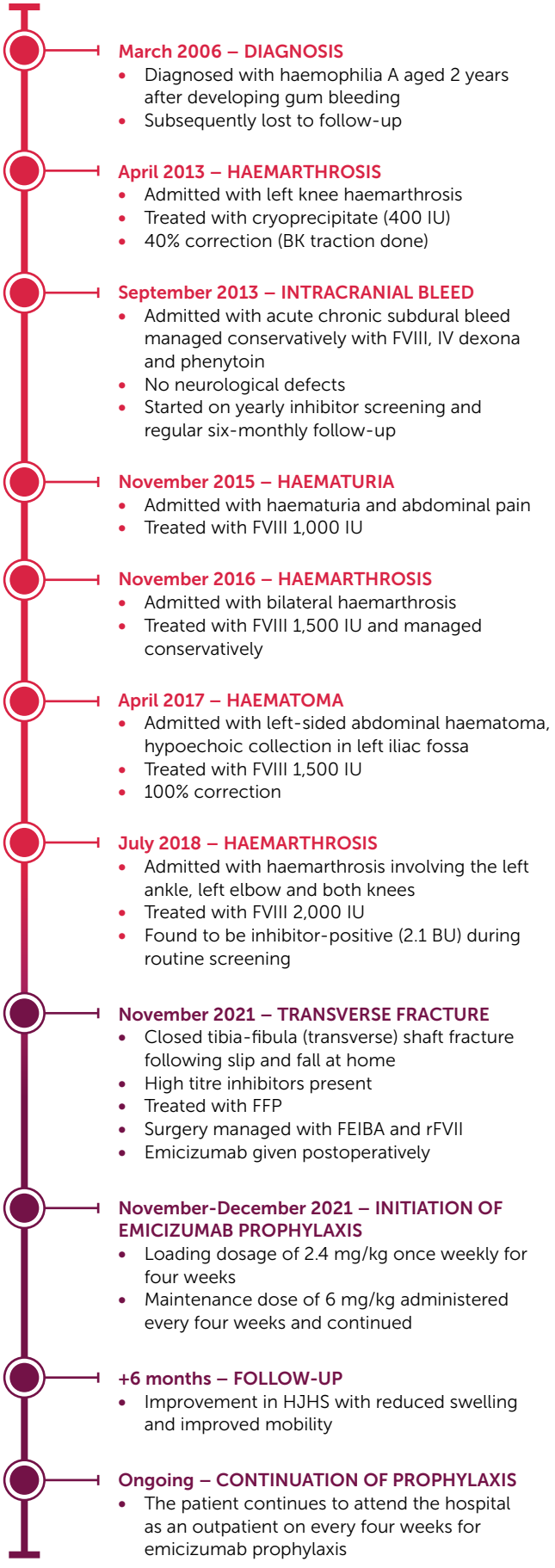


Figure 4. Haemophilia Joint Health Score (HJHS) for left knee and left ankle



J Haem Pract 2023; 10(1). doi: 10.2478/jhp-2023-0014

Figure 5. Timeline showing significant episodes in the patient's history, and treatment and management following a right closed tibia-fibula (transverse) shaft fracture



patient is a high or low responder, and whether the bleeding episode is major or minor [6,11]. Historically, the treatment of choice in major haemorrhage has varied from high-dose human FVIII concentrate, recombinant factor VII (rFVII) and FEIBA. For minor haemorrhage, rFVII and FEIBA are recommended even in low responders, as they may convert to high responders if repeatedly transfused with FVIII [11].

However, a crucial factor to be noted is the high cost of obtaining bypassing agents. Jadhav et al. reported in 2014 that in India, one injection of rFVII (NovoSeven) cost INR 43,000 (USD 518), and FEIBA cost around INR 30 (USD 0.4) per IU, with at least 1,000 units required to achieve haemostasis (INR 30,0000 / USD 361.5) [13]. As the average per capita income is around INR 170,000 per annum (ca. USD 2,047) this represents a major hurdle, as the average cost of managing a single major bleeding episode is difficult for most of the population to pay out-of-pocket [14]. Bypassing agents are ordered by hospitals upon payment by the patient, and most hospitals do not store them due to their high costs. Due to lack of access to treatment products and inability to pay, treatment is frequently delayed and bypassing agents are often infused in doses that are too low [13].

In the case presented here, we would ideally have liked to start bypassing agents at the time the patient was admitted as he was known to have inhibitors. However, as he came from a low-income household, we had to manage haemostasis with FFP and antifibrinolytic agents until funds to obtain bypassing agents were made available through an appeal to local haemophilia societies. Once this was arranged, treatment with FEIBA was started as described above. In low-resource countries where financial constraints result in a lack of treatment options, innovative management options must be considered to deal with such complications.

Although concomitant use of FEIBA and rFVII (NovoSeven) has been shown to be very effective, combination treatment is only recommended in serious life-threatening bleeds because of the increased risk of thrombosis [6,7]. Due to resource constraints, in the case reported here we used a combination of low-dose FEIBA with rFVII. The activated proteases that provide pro-coagulant activity in FEIBA have a short half-life [15]; as we used lower than the recommended dose, there was a risk of breakthrough bleeding between doses that would have been problematic during surgery. Alongside the delayed administration of these products, the benefits of the combination of both bypassing agents exceeded the risks of thrombosis.

Non-factor replacement (NFR) therapies that can be administered subcutaneously are now standard of care as prevention therapy in PwHA with inhibitors. One such example is emicizumab, a recombinant, humanised, bispecific monoclonal antibody, which binds to activated factor IX (FIXa) and factor X (FX), thereby mimicking the cofactor function of activated FVIII [16]. A phase 3 trial (HAVEN 3) assessing prophylactic emicizumab regimens administered once weekly versus no prophylaxis in PwHA without inhibitors resulted in bleeding rates that were significantly lower (more than 95%) than with no prophylaxis [17]. However, bypassing agents such as emicizumab are less effective than FVIII concentrates in treating major traumatic bleeds or as a therapeutic to support patients during surgery, as their protection against bleeding is only partial [3,18]. Some studies recommend the use of a traditional bypassing agent (FEIBA) in surgery for patients with inhibitor-positive haemophilia A to maintain haemostatic control as a first-line haemostatic agent is recommended [7]. FEIBA contains proenzymes of the prothrombin complex factors prothrombin, FVII, FIX and FX, and controls bleeding by induction and facilitation of thrombin generation [19]. Long-term use of FEIBA is associated with thromboembolic complications, and severe adverse events including overt disseminated intravascular coagulation (DIC) and myocardial infarction. Patients with a high titre inhibitor may be unresponsive to treatment with FEIBA [20,21]. The use of emicizumab concomitantly with FEIBA has been shown to improve response in such cases but can also rarely be associated with thromboembolic events [18,22]. The availability of emicizumab in clinical practice is progressively increasing the number of patients treated and clinicians' knowledge of this drug. Breakthrough bleeds may still occur (e.g. in trauma, emergency surgery) and co-administration of FEIBA may be required, with potential prothrombotic risk [18].

World Federation of Hemophilia (WFH) guidelines recommend prophylactic dosing with emicizumab consists of an induction period of 3.0 mg/kg/week for four weeks by subcutaneous injection, followed thereafter by 1.5 mg/kg/week or alternative dosing schedules including 3 mg/kg every two weeks or 6 mg/kg every four weeks [2]. Consensus recommendations of the Indian Academy of Pediatrics note the effectiveness of emicizumab in preventing bleeds, however implementation of a prophylactic programme is not routine [5]. Its cost (INR 87,000 for 60 mg injection) makes its availability to the general population of India a challenge. There is a lack of published literature on the use of emicizumab in India, but it has been shown to be effective and safe in Indian children and has the potential to improve the quality of life of inhibitor-positive patients who otherwise have high morbidity [23].

CONCLUSION

Novel modalities of treating PwH with inhibitors are being developed and tested worldwide. However, treating such patients in emergency scenarios is a daunting task. The use of emicizumab for routine prophylaxis to protect against bleeds in PwHA with inhibitors has been explored in many countries with largely positive results. Its use alongside bypassing agents such as FEIBA to facilitate haemostasis in emergency scenarios is limited but has shown positive results in the case presented and has the potential to improve the quality of life of these patients.

Even with the advent of newer treatment options, PwHA in India face numerous hurdles, especially those who are inhibitor-positive. Treatment of a single bleeding episode can cost families an exorbitant amount, which many are unable to afford. Haemophilia societies have been vitally important in efforts to make novel treatments available to families in need, but easy access to treatment remains a challenge.

ACKNOWLEDGEMENTS

The authors have advised no interests that might be perceived as posing a conflict or bias.

Informed consent has been obtained from the individual reported in this case study.

ORCID

Simran Bhatia https://orcid.org/0009-0009-2738-655X
Archana M V https://orcid.org/0000-0002-7616-6408
Ganesh M Balthillya https://orcid.org/0000-0002-2249-0181
Vasudeva Bhat https://orcid.org/0000-0002-4081-1372
Sulochana Badagabettu https://orcid.org/0000-0002-2242-3413

REFERENCES

1. Pinto P, Shelar T, Nawadkar V, et al. The epidemiology of FVIII Inhibitors in Indian haemophilia A patients. *Indian J Hematol Blood Transfus* 2014; 30(4): 356-63. doi: 10.1007/s12288-014-0342-z.
2. Srivastava A, Santagostino E, Dougall A, et al. WFH Guidelines for the Management of Hemophilia, 3rd edition. *Haemophilia* 2020; 26(S6): 1-158. doi: 10.1111/hae.14046.
3. Pratt KP, Arruda VR, Lacroix-Desmazes S. Inhibitors – Recent insights. *Haemophilia* 2021; 27 Suppl 3: 28-36. doi: 10.1111/hae.14077.
4. Peyvandi F, Mannucci PM, Garagiola I, et al. A randomized trial of factor VIII and neutralizing antibodies in hemophilia *A. N Engl J Med* 2016; 374(21): 2054-64. doi: 10.1056/NEJMoa1516437.

5. Sachdeva A, Gunasekaran V, Ramya HN, et al. Consensus Statement of the Indian Academy of Pediatrics in Diagnosis and Management of Hemophilia. *Indian Pediatr* 2018; 55(7): 582-90. doi: 10.1007/s13312-018-1302-8.
6. Phadke S. Hemophilia care in India: a review and experience from a tertiary care centre in Uttar Pradesh. *Indian J Hematol Blood Transfus* 2011; 27(3): 121-6. doi: 10.1007/s12288-011-0084-0.
7. Rangarajan S, Austin S, Goddard NJ, et al. Consensus recommendations for the use of FEIBA(®) in haemophilia A patients with inhibitors undergoing elective orthopaedic and non-orthopaedic surgery. *Haemophilia* 2013; 19(2): 294-303. doi: 10.1111/hae.12028.
8. Ghosh K, Shetty S, Kulkarni B, et al. Development of inhibitors in patients with haemophilia from India. *Haemophilia* 2001; 7(3): 273-8. doi: 10.1046/j.1365-2516.2001.00505.x.
9. Kumar S, Sinha S, Bharti A, Meena LP, Gupta V, Shukla J. A study to determine the prevalence, clinical profile and incidence of formation of inhibitors in patients of hemophilia in North Eastern part of India. *J Family Med Prim Care* 2019; 8(7): 2463-7. doi: 10.4103/jfmpc.jfmpc_316_19.
10. Shah S, Patel T, Bhatnagar N, Gajjar M, Shah M, Tripathi S. "Prevalence of Inhibitors in Hemophilia Patients and its Clinical Implications": A study of 276 patients in Western India. *Global Journal of Transfusion Medicine* 2019; 4(2): 168. doi: 10.4103/GJTM.GJTM_35_19.
11. Lichtman M, Kaushansky K, Prchal J, Levi M, Burns L, Linch DC. *Williams Manual of Hematology*, 10th edn. 2022. Columbus, OH: McGraw-Hill Education.
12. Verbruggen B. Diagnosis and quantification of factor VIII inhibitors. *Haemophilia* 2010; 16(102): 20-4. doi: 10.1111/j.1365-2516.2008.01924.x.
13. Jadhav U, Mukherjee K, Lalwani A. Ethical issues in the care of persons living with haemophilia in India. *Indian J Med Ethics* 2014; 11(4): 223-7. doi: 10.20529/IJME.2014.056.
14. Per capita national income across India from financial year 2015 to 2018, with estimates until 2023. Statista. 23 August 2023. Available from: *https://www.statista.com/statistics/802122/india-net-national-income-per-capita/* (accessed 14 September 2023).
15. Malkan UY, Aksu S. Combination of NovoSeven and FEIBA in hemophiliac patients with inhibitors. *Open Med* (Wars) 2018; 13: 618-21. doi: 10.1515/med-2018-0090.
16. Berntorp E, Hermans C, Solms A, Poulsen L, Mancuso ME. Optimising prophylaxis in haemophilia A: The ups and downs of treatment. *Blood Rev* 2021; 50: 100852. doi: 10.1016/j.blre.2021.100852.
17. Mahlangu J, Oldenburg J, Paz-Priel I, et al. Emicizumab prophylaxis in patients who have hemophilia a without inhibitors. *N Engl J Med* 2018; 379(9): 811-22. doi: 10.1056/NEJMoa1803550.
18. Linari S, Castaman G. Concomitant use of rFVIIa and emicizumab in people with hemophilia A with inhibitors: current perspectives and emerging clinical evidence. *Ther Clin Risk Manag* 2020; 16: 461-9. doi: 10.2147/TCRM.S205310.
19. Turecek PL, Váradi K, Gritsch H, Schwarz HP. FEIBA: mode of action. *Haemophilia* 2004; 10 Suppl 2: 3-9. doi: 10.1111/j.1365-2516.2004.00934.x.
20. Collins PW, Liesner R, Makris M, et al. Treatment of bleeding episodes in haemophilia A complicated by a factor VIII inhibitor in patients receiving Emicizumab. Interim guidance from UKHCDO Inhibitor Working Party and Executive Committee. *Haemophilia* 2018; 24(3): 344-7. doi: 10.1111/hae.13495.
21. Hayashi T, Tanaka I, Shima M, et al. Unresponsiveness to factor VIII inhibitor bypassing agents during haemostatic treatment for life-threatening massive bleeding in a patient with haemophilia A and a high responding inhibitor. *Haemophilia* 2004; 10(4): 397-400. doi: 10.1111/j.1365-2516.2004.00924.x.
22. Kizilocak H, Marquez-Casas E, Malvar J, Young G. Safety of FEIBA and emicizumab (SAFE): Dose escalation study evaluating the safety of in vivo administration of activated prothrombin complex concentrate in haemophilia A patients on emicizumab. *Haemophilia* 2023; 29(1): 100-5. doi: 10.1111/hae.14684.
23. Radhakrishnan N, Shankar R, Maji M, Rana M. Initial experience of Emicizumab prophylaxis in children with inhibitor positive severe hemophilia A from a single center in India. *Pediatric Hematology Oncology Journal* 2021; 6(2):97-9. doi: 10.1016/j.phoj.2021.03.004.

HOW TO CITE THIS ARTICLE:
Bhatia S, M V A, Balthillya GM, Bhat V, Badagabettu S. A creative approach to managing a case of haemophilia A with inhibitors in a low-resource country: case report. *J Haem Pract* 2023; 10(1): 82-89. *https://doi.org/10.2478/jhp-2023-0014*