Received: 3 May 2022 | Revised: 5 August 2022 | Accepted: 6 November 2022

DOI: 10.1111/bcp.15598

SHORT COMMUNICATION

Management of acquired haemophilia A in severe Covid-19: Haemostatic bridging with emicizumab to keep the balance between bleeding and thrombosis

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Acquired haemophilia A (AHA) is an autoimmune bleeding disorder caused by autoantibodies blocking coagulation factor VIII (FVIII). Haemostatic management of AHA and concomitant thrombotic risk is difficult. We cover the management of a 75-year-old male with severe Covid-19, a prothrombotic disease, and de novo AHA with severe muscle bleeding, a disease requiring highly thrombogenic haemostatic therapy and immunosuppression—a challenging combination. FVIII activity was measured using human and bovine reagents to differentiate between endo- and exogenous FVIII activity. For haemostatic control, recombinant human activated FVII was given, followed by emicizumab, as a less thrombogenic long-term haemostatic agent. Steroids were used as initial immunosuppressive therapy. Later, rituximab was used for inhibitor eradication. No thromboembolic events occurred, and bleeding was effectively controlled. Emicizumab achieved haemostatic balance in a patient under haemorrhagic and thrombogenic conditions. Individual risk assessment is needed to guide treatment decisions in patients threatened by simultaneous bleeding and thrombosis.

KEYWORDS
acquired haemophilia A, bleeding, coagulation, Covid-19, emicizumab, thrombosis

1 | INTRODUCTION

Since December 2019, a novel coronavirus, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has ravaged the planet, causing primarily respiratory infections ranging from asymptomatic or mild forms all the way to acute respiratory distress syndrome necessitating intensive care. However, coronavirus disease 2019 (Covid-19) has also been associated with a significant activation of the coagulation system and thromboembolic events, and prophylactic anticoagulation is recommended for inpatient care.[1,2]

Acquired haemophilia A (AHA) is a rare autoimmune bleeding disorder, which is caused by inhibiting autoantibodies to coagulation factor VIII (FVIII).[3] Skin and deep tissue (musculoskeletal and retroperitoneal) bleedings represent the typical bleeding pattern of AHA.[4] A higher inhibitor titre is associated with more severe bleeding and a higher risk of deep tissue bleedings.[4] Treatment objectives in AHA involve the control and prevention of bleeding and inhibitor elimination.[5] Bleeding control using bypassing agents is effective in >90% of patients.[6] In contrast, a rate of 2.7% of thromboembolic events in bleeding patients receiving haemostatic therapy is reported.[6] However, acute illness and immobility increase the risk of

thromboembolic events in bleeding AHA patients. Emicizumab, a bispecific antibody mimicking the function of FVIII, presents an emerging treatment strategy in patients with congenital haemophilia A, but experience in its use in patients with AHA is based on small case series only.[7,8]

Here, we present a bleeding patient with de novo diagnosed AHA and Covid-19, who is threatened by both haemorrhagic and thromboembolic events, but also by potential complications from immunosuppression.

What is already known about this subject?

- Treatment experience with emicizumab in acquired haemophilia A is limited.
- Covid-19 is associated with severe inflammation, thromboembolic events and organ damage.
- The management of simultaneous haemorrhagic and thrombogenic states is challenging.

What this study adds?

- Emicizumab, in combination with short-term rhFVIIa, achieved haemostatic balance in a bleeding patient with acquired haemophilia A and severe Covid-19.
- Emicizumab may be used in patients with acquired haemophilia A who are at high risk of both haemorrhagic and thromboembolic events.
- Individual risk assessment is needed to guide haemostatic treatment or anticoagulation in patients simultaneously threatened by bleeding and thrombosis.

2 | METHODS

The patient agreed to the off-label use and advantages and disadvantages of emicizumab and rituximab in his condition. Written informed consent was obtained from the patient for anonymized publication of this case. The need for an institutional ethics review was waived, as this treatment was not performed within a clinical trial.

2.1 | FVIII activity

Prior to emicizumab exposure, FVIII activity was measured using a standard one-stage clotting assay. After start of emicizumab, FVIII activity was measured with the chromogenic Biophen FVIII coagulation activity assay (Hyphen, Neuville-sur-Oise, France) using human reagents (FVIII:h), which detect endogenous FVIII activity and are also sensitive to the effects of emicizumab. In addition, a chromogenic FVIII activity assay using bovine reagents, insensitive to emicizumab, was used to solely detect the patient's own FVIII activity (FVIII:b).[8] All FVIII activity measurements were performed on a CS-5100 analyser (Siemens, Marburg, Germany). Emicizumab dosing was guided according to FVIII levels as described previously.[8]

2.2 | FVIII inhibitor titre

FVIII inhibitor titres were quantified with the Nijmegen-modified Bethesda method using the one-stage FVIII clotting assay. After treatment start with emicizumab, the chromogenic FVIII activity assay including bovine reagents was used for the Bethesda assay.

2.3 | Emicizumab dosing

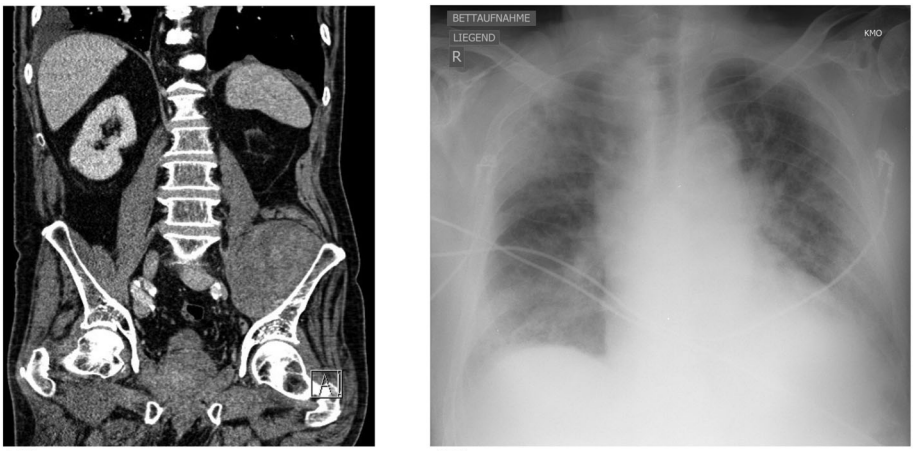
Emicizumab dosing was performed as reported previously.[8] Initial dosing was done with subcutaneous emicizumab 3 mg/kg bodyweight weekly for the first 3 weeks, thereafter with 1.5 mg/kg body weight every 2–4 weeks until remission. FVIII:h and FVIII:b were regularly assessed and a range of FVIII:h 10–30% was targeted for emiczumab dosing, and FVIII:b to detect remission (>50%).

3 | RESULTS

3.1 | History and findings on admission

A 75-year-old male patient with Covid-19 was admitted to the University Hospital of Vienna because of respiratory failure and major bleeding of his left psoas muscle (Figure 1). He had a history of ST-elevation myocardial infarction with coronary stenting 6 months earlier, arterial hypertension, hyperlipidaemia and an infrarenal aortic aneurysm.

One month before admission, the patient complained about pain in his left groin. A computed tomography (CT) scan revealed a large haematoma in the iliacus muscle (15 × 7.5 × 4.5 cm). Dual antiplatelet therapy was temporarily discontinued, but the haemoglobin level dropped from 10.3 to 8.2 g/dL within 48 h, fulfilling the criteria of major bleeding.[9] Two units of packed red blood cells were transfused. Despite an isolated prolonged activated partial thromboplastin time (APTT), no further coagulation studies were done and the patient was discharged with a single antiplatelet regimen consisting of clopidogrel. Two days before admission (= Day 1) the patient reported to another hospital because of dyspnoea and worsening pain and was tested positive for SARS-CoV-2 on a PCR assay. A CT scan revealed a new haematoma in the right pectineus muscle, the haemoglobin level was 6.9 g/dL. Now, further coagulation studies revealed a FVIII activity <1%, suggesting AHA. The patient was transferred to the University Hospital of Vienna for further management. A full description of the clinical and laboratory findings is provided in the Supporting information.



(A) (B)

FIGURE 1 Computed tomography scan and chest radiograph. (A) CT scan 7 days before admission to the external hospital. It shows a large haematoma within the left iliopsoas muscle, 10.3 × 7 × 9.3 cm. (B) Chest X-ray at the first day of intensive care (Day 10). It shows multiple streaky-patchy opacities compatible with pneumonic consolidations, particularly in the suprabasal lung sections and the right upper field.

On admission (= Day 4), the patient was in moderate respiratory distress and needed nasal oxygen support to maintain adequate peripheral oxygen saturation levels. The chest x-ray revealed bilateral pneumonia (Figure 1). He had severe anaemia (haemoglobin 7.4 g/dL), a prolonged APTT (128 s), FVIII activity <1%, FVIII inhibitor titre (bovine) 41.8 Bethesda units (BU)/mL, von Willebrand factor antigen 179%.

Antiplatelet treatment was stopped and haemostatic therapy with reduced dose (50 mcg/kg body weight every 3 h) recombinant human activated FVII (rhFVIIa; NovoSeven®, Novo Nordisk, Denmark) started. Recombinant porcine FVIII (rpFVIII) concentrate was considered, but not chosen due to possible cross-reactivity of FVIII inhibitors with porcine FVIII, especially in case of a high inhibitor titre (>20 BU/mL),[10] and the expected long duration of haemostatic therapy. For haemostatic control and prevention of further bleeding, weekly subcutaneous emicizumab (3 mg/kg; Hemlibra®, Roche, Switzerland) was started on Day 5. For treatment of Covid-19, remdesivir (Day 4) and convalescent plasma (Day 5) were given. For both immunomodulation in Covid-19 and inhibitor eradication in AHA, treatment with glucocorticoids (prednisone 100 mg, then dexamethasone 6 mg) was initiated on Day 4. Key laboratory results and treatment interventions are shown in Figure 2.

3.2 | Clinical course and treatment response

Concomitant use of rhFVIIa and emicizumab did not cause any thromboembolic events or thrombotic microangiopathy. Under continued treatment with glucocorticoids, FVIII inhibitor levels decreased slightly, but endogenous FVIII activity remained low (Figure 3). During therapy with emicizumab, no further bleeding episodes occurred.

The patient was switched to high-flow nasal oxygen support (AIRVO 2, Fisher & Paykel Healthcare, New Zealand) because of further respiratory deterioration and was transferred to the intensive care unit (Days 10–15), but needed no intubation. He was discharged on Day 21 with limited mobility, still relying on ambulatory oxygen insufflation indicating Covid-19-associated chronic lung damage. Additional clinical, laboratory and radiologic findings are provided in the Supporting information.

After discharge, the patient repeatedly tested positive for anti-SARS-CoV-2 antibodies (Day 26, Day 33, Day 47), thus it seemed safe to use rituximab (MabThera®, Roche, Switzerland) because of re-increasing FVIII inhibitor levels at Day 47. Subsequently, a rapid increase of FVIII activity occurred, achieving complete remission (defined as FVIII:b > 50%, no active bleeding after stopping any haemostatic drug for >24 h and a negative inhibitor test) between Days 82 and 110 (Figure 3).[11] Antiplatelet treatment with clopidogrel was re-started as soon as the FVIII:b exceeded 50%.

4 | DISCUSSION

The therapeutic dilemma of a patient who is simultaneously threatened by both thromboembolic events and overt bleeding remains challenging. This patient presented with severe muscle bleeding due to AHA, which was complicated by the onset of severe Covid-19. Since prolongation of APTT was present even before SARS-CoV-2 infection, Covid-19-induced AHA was unlikely. While the overt bleeding situation calls for urgent haemostatic support, antithrombotic treatment for both Covid-19 (prophylactic anticoagulation) and recent coronary stent implantation (dual antiplatelet therapy) would be needed. Covid-19 is associated with an increased thrombogenic risk, which is presumably increased in cases of massive inflammation.[12]

Treatment of bleeding in AHA requires the use of bypassing agents (rhFVIIa or activated prothrombin complex concentrates), which are associated with an increased prothrombotic risk, especially in patients with risk factors or recent thromboembolic events.[5,6] In our patient, due to acute inflammatory disease and a known highly thrombogenic state, the risk of thromboembolism with bypassing agents was expected to be high. In addition, our patient was at increased risk of stent thrombosis, as dual antiplatelet therapy had to be stopped temporarily.

However, bleeding control needs to be prioritized and time to treatment should not be delayed. We recently generated

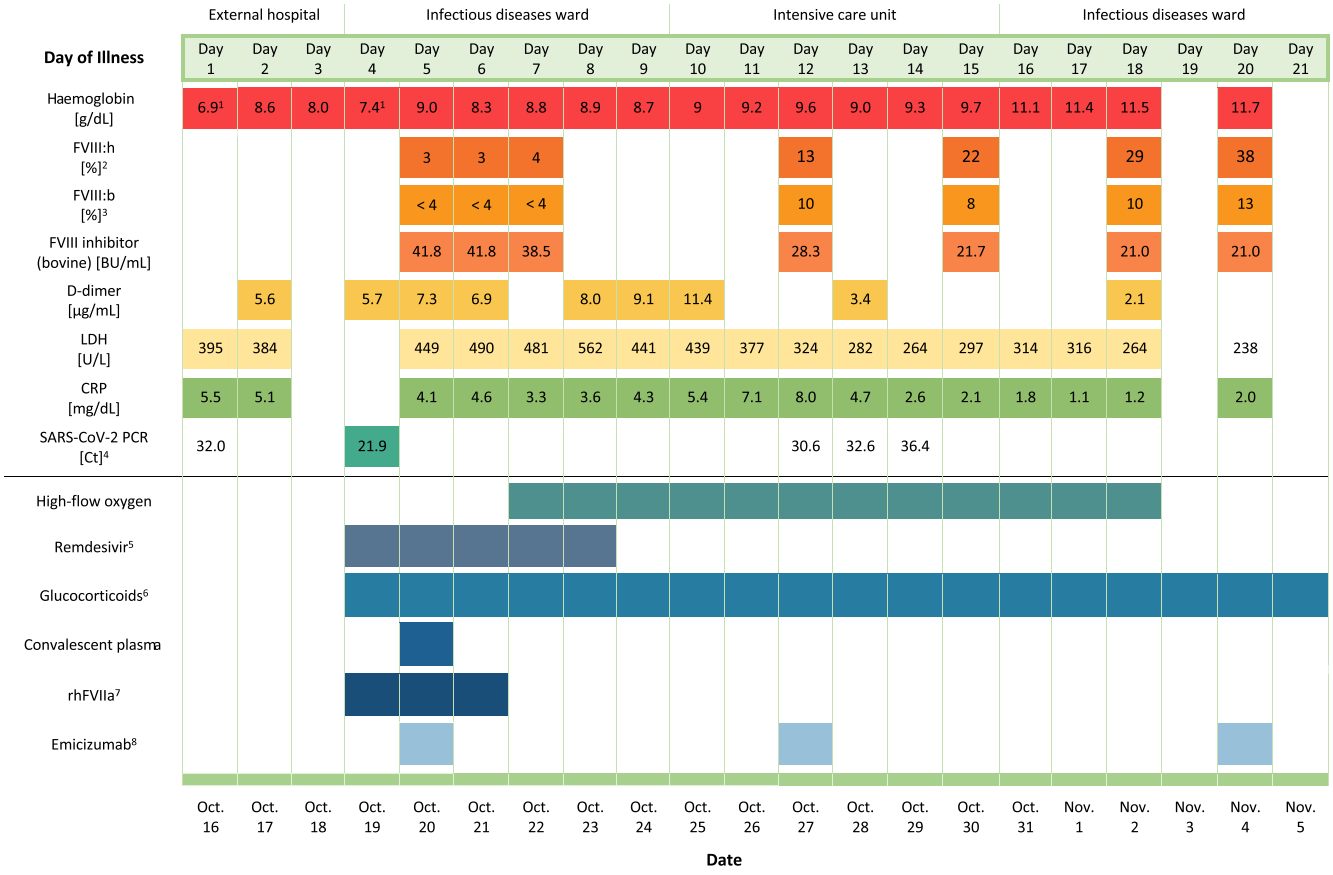


FIGURE 2 Key laboratory results and treatment interventions from Day 1 of illness to hospital discharge. A coloured background indicates that the laboratory result is out of the normal range. (1) Packed red blood cells (RBC); (2) FVIII activity measured with a chromogenic assay using human reagents to assess the pharmacodynamic effect of emicizumab (FVIII:h, normal range: 50%–200%); (3) FVIII activity measured with a chromogenic assay using bovine reagents to assess endogenous FVIII activity (FVIII:b, normal range: 70%–150%); (4) Cycle threshold; (5) Remdesivir (Veklury®) was given at an initial loading dose of 200 mg and then followed up by a daily maintenance dose of 100 mg for a total treatment duration of 5 days; (6) Treatment with glucocorticoids was initiated on the first day of admission with prednisone 100 mg once daily and was switched on Day 11 to dexamethasone 6 mg due the patient's worsening respiratory condition; (7) Recombinant human activated FVII (rhFVIIa; Novoseven®) 5 mg (approximately 50 µg/kg) was initially given every 3 h (8 doses total), then 4 mg (approximately 40 µg/kg) every 4 h (6 doses total); (8) Emicizumab 210 mg (3 mg/kg) was given once weekly, three times during the patient's admission to the hospital.

experience with emicizumab for AHA.[8] Emicizumab is a humanized bispecific FVIII-mimetic therapeutic antibody, approved for prophylaxis of bleeding in haemophiliacs with and without inhibitors.[13,14] We learned that even in AHA with severe bleeding, bleeding control was achieved after median 4 days after the first subcutaneous injection, without any re-bleeding observed. The use of emicizumab seems advantageous since it is administered subcutaneously, has a long-lasting haemostatic efficacy and an expected low thrombogenicity.[15] However, assessment of coagulation function under emicizumab is complicated and its use is currently not approved for AHA.

Limited treatment experience in AHA, including emicizumab, precludes substantiated, evidence-based decision-making in the management of co-occurring bleeding and thrombosis. In patients with severe bleeding disorders such as AHA, management of bleeding and thrombosis is difficult and the decision how to treat is often based on an assessment of individual haemorrhagic and thromboembolic risk. Due to lack of data for AHA, some lessons may be learned from patients with congenital haemophilia with and without inhibitors. In these patients, the use of antiplatelets and anticoagulants is generally contraindicated,[16] which limits therapeutic choices in the event of thromboembolism or need for anticoagulation. According to treatment recommendations for AHA, antithrombotic treatment can safely be initiated once endogenous FVIII levels reach normal levels.[5] In patients with AHA under bridging treatment with emicizumab with still low FVIII:b levels, we would still argue not to administer antithrombotic treatment because of a remaining risk of bleeding in the presence of inhibitors.

Considering emicizumab's expected low thromboembolic risk, its limited treatment experience in AHA and its use in a proinflammatory state cannot fully exclude any prothrombotic tendencies.

Co-occurring bleeding and thrombosis in AHA represent a challenge that requires careful risk assessment of opposing threats. In patients undergoing treatment with emicizumab, reduced dose

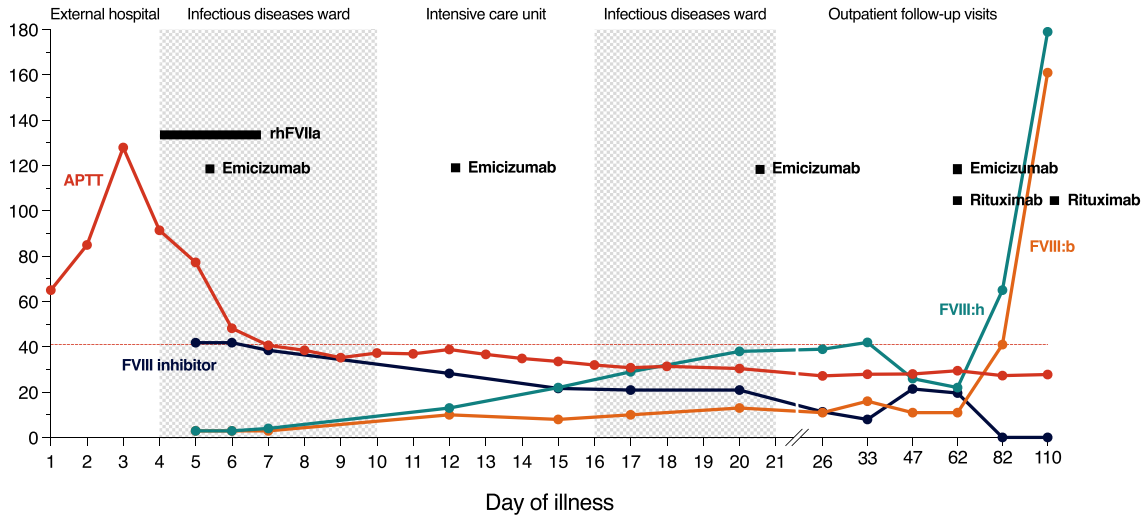


FIGURE 3 Course of coagulation markers. Treatment with rhFVIIa was initiated on the day of admission (Day 4) to counteract the muscle bleeding. On the following day (Day 5), treatment with emicizumab (210 mg = 3 mg/kg) was started. Activated partial thromboplastin time (APTT) cannot be used as parameter for pharmacodynamic response to emicizumab as emicizumab artificially lowers APTT values. Immunosuppressive treatment with prednisone was initiated on Day 4 and was subsequently changed to dexamethasone on Day 11. FVIII inhibitor levels decreased until Day 33, while endogenous FVIII activity failed to increase adequately. Because of rising FVIII inhibitor levels on Day 47, immunosuppressive treatment with rituximab was started on Day 62. Subsequently, FVIII inhibitor levels decreased and FVIII activity increased, resulting in a complete response approximately 4 weeks after treatment initiation. APTT [s], FVIII inhibitor (bovine) [BU/mL], FVIII:h [%], FVIII:b [%].

rhFVIIa could be used for acute bleeding, but this combination could be thrombogenic. In patients with low titre FVIII inhibitors, replacement with appropriately dosed human or porcine FVIII concentrates is probably a good choice, as FVIII has a much higher affinity for FIXa and FX and supersedes emicizumab from these binding sites, but further studies are needed to clarify these points.

Immunosuppression is the treatment of choice to eliminate the FVIII-directed autoantibodies.[4] The recommended treatment for Covid-19 involves the use glucocorticoids, which are also part of immunosuppressive strategies, recommended for the elimination of the FVIII inhibitor. However, an inhibitor titre of >20 BU/mL is predictive for a prolonged time until remission and would require more intensive immunosuppression with corticosteroids plus rituximab or a cytotoxic agent.[5] Overt Covid-19 renders the use of rituximab or cytotoxic agents impossible because it may lead to disease progression (potentially entailing intravenous lines, intubation or extracorporeal membrane oxygenation, all of them bearing a high risk of severe bleeding complications) thereby precluding timely inhibitor eradication. However, as long as FVIII concentration is low, the risk of bleeding is high.[17] Conceivably, the treatment objective in this case was to stop and prevent bleeding without creating too much prothrombotic risk and to bridge the critical time frame until immunosuppressive treatment can safely be started. The safety and efficacy of emicizumab in AHA is currently being investigated in two ongoing clinical trials, NCT04188639 and NCT05345197.

In summary, this report showcases that severe bleeding in AHA under a simultaneous thrombogenic state can be successfully treated with rhFVIIa and emicizumab without causing thromboembolic events. Finally, this case study underscores the potential of emicizumab for use in AHA and advocates individual risk assessment of bleeding and thrombosis to guide haemostatic treatment or anticoagulation.

ACKNOWLEDGMENTS

We thank all physicians and nurses involved in the clinical treatment of the patient and the staff of the coagulation laboratory for their excellent technical assistance.

COMPETING INTERESTS

P.K. has received research funding, travel grants and consultancy fees from Novo Nordisk, Takeda/Shire and Roche. The other authors declare no relevant conflicts of interest.

CONTRIBUTORS

Georg Gelbenegger and Paul Knöbl wrote the manuscript. Georg Gelbenegger, Ludwig Traby and Paul Knöbl analysed clinical data. Georg Gelbenegger and Nina Rahimi created tables and figures. Georg Gelbenegger, Ludwig Traby, Nina Rahimi and Paul Knöbl critically revised the manuscript.

DATA AVAILABILITY STATEMENT

Data can be made available upon request to the corresponding author.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Gelbenegger G, Traby L, Rahimi N, Knöbl P. Management of acquired haemophilia A in severe Covid-19: Haemostatic bridging with emicizumab to keep the balance between bleeding and thrombosis. *Br J Clin Pharmacol*. 2023;89(2):908-913. doi:10.1111/bcp.15598