

# **“Don’t Add Fuel to the Fire”– Hyperhemolysis Syndrome in a Pregnant Woman with Compound Sickle Cell Disease/ $\beta^0$ -Thalassemia: Case Report and Review of the Literature**

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## **Keywords**

Hemoglobinopathies · Hyperhemolysis · Pregnancy · Sickle cell disease and thalassemia

## **Abstract**

Hyperhemolysis syndrome (HHS) is a rare and severe posttransfusion complication characterized by the destruction of both recipient and donor red blood cells. The underlying mechanism of HHS is not fully understood and proper management can be difficult. Furthermore, there are few reports regarding HHS in pregnancy. We report on the development and management of HHS in a pregnant woman with known compound sickle cell disease (SCD)/ $\beta^0$ -thalassemia and alloimmunization after transfusion of packed red blood cells (PRBC). We aim to raise awareness on this diagnostically challenging and life-threatening type of hemolysis with this report, and to stress the need to consider the diagnosis of HHS in SCD patients with progressive anemia despite PRBC administration.

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## **Introduction**

Sickle cell disease (SCD) is a hemoglobinopathy due to a point mutation in the  $\beta$ -globin gene with autosomal recessive inheritance [1]. Patients with SCD may suffer vaso-occlusive crises (VOC) [2], acute chest syndrome, hemolysis with severe anemia, and a variety of other symptoms [3]. Treatment of these symptoms often requires transfusion therapy using either packed red blood cell (PRBC) or red blood cell (RBC) exchange transfusion [4, 5]. Some SCD patients have a high transfusion requirement, resulting in a higher susceptibility to transfusion-related complications [6]. A rare and serious transfusion-related complication is hyperhemolysis syndrome (HHS) [7–10], in which both recipient and donor RBCs are destroyed by intravascular hemolysis. In HHS, the hemoglobin (Hb)A/HbS ratio remains unchanged, and the Hb level usually falls below the pre-transfusion range [11]. Laboratory analysis revealed signs of hemolysis with elevated bilirubin, lactate dehydrogenase concentrations. Likewise, a relatively low count of reticulocytes is common [12]. In rare cases, bone marrow

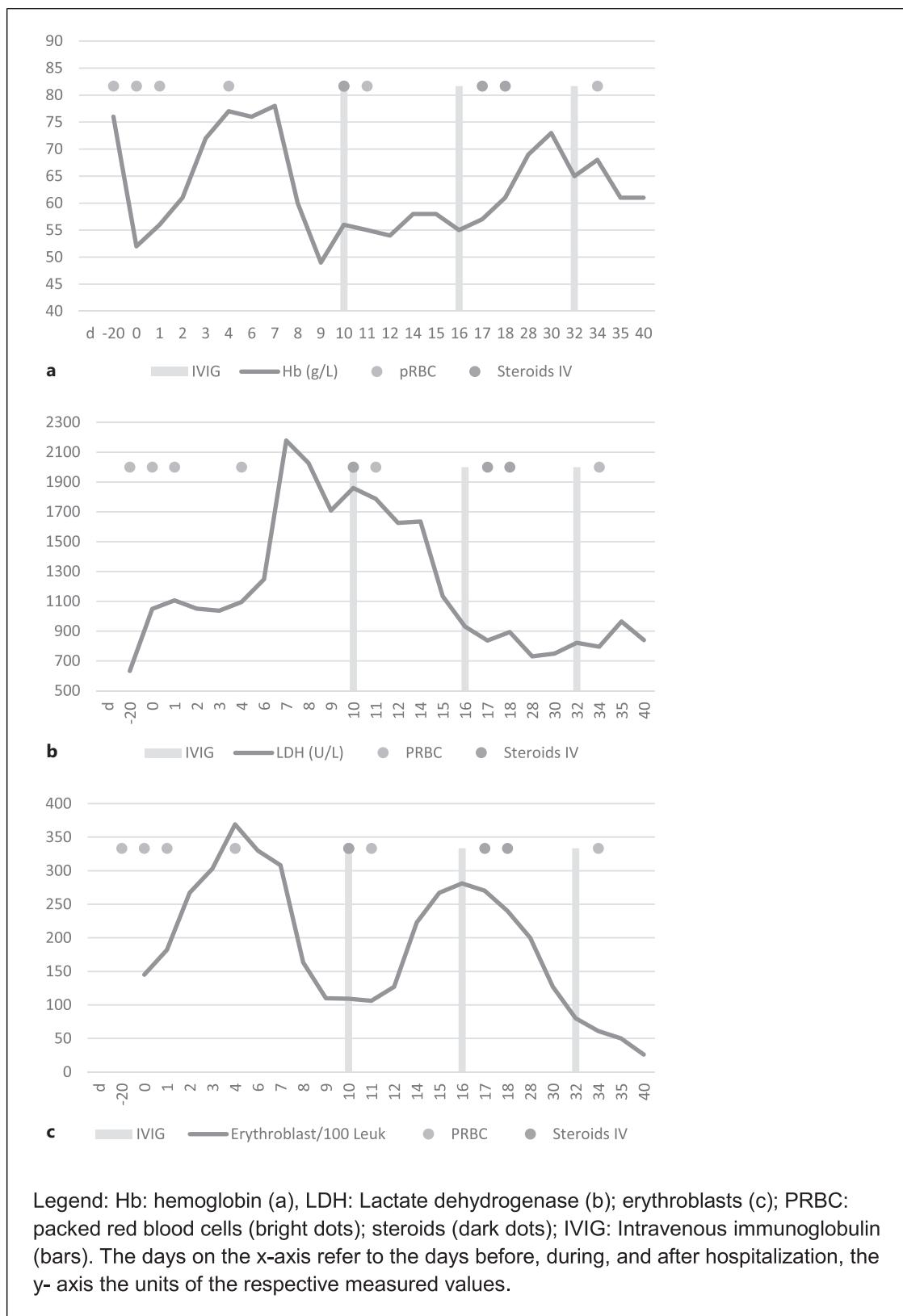
**Table 1.** Overview of the phenotypes of the pRCBs administered

Genotype patient	<i>RHD*01, RHCE*02, RHCE*03, FY*01, FY*02, JK*01, JK*02, KEL*01.01, KEL*02; GYPA*01, GYBB*04</i>		
potential phenotype patient	A RhD-pos; CcDEe, Fy(a+b+), Jk(a+b+), K+k+, M+N-S-s+		
time frame	PRBC	phenotype	patient's alloantibody profile
Age 22	Cumulative 4 PRBC tested, it is not known whether all were transfused	A RhD-pos; D+, C-, c+, E+, e+, Cw-, K-, Kp(a)-, Fy(a+b-), Unknown Jk(a-b+), Le(a+b-), M+, N+, S-, s+, P1+	
		A RhD-pos; D+, C-, c+, E+, e-, Cw-, K-, Kp(a)-, Fy(a+b+), Jk(a-b+), Le(a+b-), Lu(a-b+), M+, N+, S-, s+, P1+	
		A RhD-pos; D+, C+, c+, E-, e+, Cw-, K-, Kp(a)-, Fy(a+b+), Jk(a-b+), Le(a-b-), M+, N-, S-, s+, P1-	
		A RhD-pos; D+, C+, c+, E+, e+, Cw-, K-, Fy(a-b+), Jk(a-b+), Le(a-b+), M+, N+, S+, s+, P1+	
Day -20	PRBC 1	A RhD-pos; D+, C+, c+, E+, e+, Cw-, K-, Kp(a)-, Fy(a+b+), Jk(a+b+), Le(a-b+), Lu(a-b+), M+N-S-s+, P1+, Vel+	Anti-Cw
Day -7			Routine testing: anti-Cw, anti-N, anti-Le(b)
Day 0	PRBC 2	O RhD-pos; D+, C+, c-, E-, e+, K-, k+, Kp(a-b+), Fy(a-b+), Jk(a-b+), Le(a-b-), Lu(a-b+), M+N-S-s+, P1+, Vel+	Anti-Cw, anti-N, anti-Le(b)
Day 0	PRBC 3	A1 RhD-pos; D+, C+, c+, E-, Cw-, e+, K-, k+, Kp(a)-, Fy(a+b+), Jk(a-b+), Le(a-b-), M+N-S-s+, P1+	Anti-Cw, anti-N, anti-Le(b)
Day 1	PRBC 4	A RhD-pos; D+, C+, c+, E-, Cw-, e+, K-, k+, Kp(a)-, Fy(a+b+), Jk(a-b+), Le(a-b-), M+N-S-s+, P1+	Anti-Cw, anti-N, anti-Le(b)
Day 3	PRBC 5	O RhD-pos; D+, C-, c+, E-, e+, Cw-, K-, k+, Kp(a-b+), Fy(a-b+), Jk(a+b+), Le(a-b-), Lu(a-b+), M+N-S-s+, P1-, Vel+	Anti-Cw, anti-N, anti-Le(b)
Day 8	PRBC 6	O RhD-pos; D+, C+, c-, Cw-, E-, e+, K-k+, Kp(a-b+), Fy(a+b-), Jk(a-b+), Le(a-b-), Lu(a-b+), M+N-S-s+, P1+	Anti-Cw, anti-N, anti-Le(b) anti-Le(bH)
Day 9	PRBC 7	O RhD-neg; D+, C-, c-, Cw-, E-, e+, K-k+, Kp(a-b+), Fy(a-b+), Jk(a+b+), Le(a-b-), Lu(a-b+), M+N-S-s+, P1-	Anti-Cw, anti-N, anti-Le(b) anti-Le(bH)
Day 35	PRBC 8	O RhD-pos; D+, C+, c-, E-, e+, Cw-, K-, k+, Kp(a-b+), Fy(a+b+), Jk(a+b-), Le(a+b-), Lu(a-b+), M+N-S-s+, P1+	Anti-Cw, anti-N, anti-Le(b), anti-Lu(a), anti-Le(bH), anti-A1

The table shows the course of the transfused PRBC and their phenotypes, the alloantibodies that occurred in chronological order after transfusion, and the blood group genotype and the probable phenotype of the patient. The crossmatch of all PRBCs has shown no incompatibilities.

progenitor cells can also be damaged, affecting RBC production, leading to severe anemia. The direct anti-globulin test (DAT) is often negative, but in some cases, it can show weakly positive IgG and C3d, and new allo-antibodies are often also present [12–16]. The clinical presentation varies from fever to jaundice to pain and can be difficult to differentiate from a VOC in a SCD patient [17].

Although the exact pathogenesis of this rare complication is still not fully understood, some immunologically mediated mechanisms have been proposed [15, 18]. This could occur as either, a result of an antigen-antibody-mediated reaction leading to hemolysis, or a mechanism with sensitization of erythrocytes by complement and/or macrophages activation [18–20]. The main known predisposing risk factors for HHS are transfusion and



**Fig. 1.** Overview of the progression over time of Hb, lactate dehydrogenase, and erythroblasts.

**Table 2.** Overview of the Hb curve (Hb, HbS, HbF, HbA)

Type of Hb	Unit	Days to admission			
		d -105	d +1	d +15	d +50
Hb	g/L	86	69	81	73
HbS	%	73.4	59.7	74.5	86.0
HbF	%	16.3	7.6	4.9	4.3
HbA	%		23.9	11.4	

hemoglobinopathies but certain factors such as multiple alloimmunizations [11, 15, 20, 21], non-B blood type and compound  $\beta^0$ -thalassemia have been theorized to play a role in exacerbating the risk of developing HHS [13, 20]. A genetic predisposition has also been proposed as a risk factor, as not every SCD patient develops HHS [14]. We report a case of a pregnant patient with compound SCD/ $\beta^0$ -thalassemia who presented with symptomatic anemia and developed a delayed form of HHS after a transfusion of PRBC with N+ and Le(b)+ antigens, the patient being negative for these [21].

## Case Report

### Medical History, Diagnostics, and Transfusion Management

We present a 36-year-old female patient, who was diagnosed with SCD/ $\beta^0$ -thalassemia at 8 years old and has since suffered 7 episodes of VOC. She was treated with hydroxycarbamide, which controlled the VOC crises and increased her HbF to a maximum value of 30.7%. Her normal Hb values were around 80 g/L (121–154 g/L). At the age of 22, she received transfusions on two occasions, and the transfusion history prior to this is unknown (Table 1).

At 26 weeks of gestation, she presented with symptomatic anemia, recurrent pain, and a Hb level of 76 g/L. Given the risk of increased morbidity in pregnancy due to severe anemia, she was transfused with a PRBC, phenotype: A RhD positive, C+ c+ E+ e+ Cw- K- Kp(a-) Fy(a+b-) Jk(a+b+) Le(a-b+) Lu(a-b+) M+N+S- s+ P1+ Vel+ (see Fig. 1, day -20 before admission). The pheno-/genotype (genotyping was performed on day 3 of the hospitalization) of the patient is as follows: RHD\*01, RHCE\*02, RHCE\*03, FY\*01, FY\*02, JK\*01, JK\*02, KEL\*01.01, KEL\*02; GYPA\*01, GYBB\*04 (probable phenotype deduced from genotype: C+c+D+E+e+, Fy(a+b+), Jk(a+b+), K+k+, M+N-S-s+). A pre-transfusion antibody screening test showed an anti-Cw alloantibody (Table 1). Three weeks after the transfusion, the patient was admitted to the hospital (admission day 0) due to marked fatigue. She was severely anemic with a Hb of 52 g/L, had a slightly elevated lactate dehydrogenase of 1,037 U/L (<480 U/L) (Fig. 1), undetectable haptoglobin (<0.10 g/L), and a normal bilirubin of 10  $\mu$ mol/L (<17  $\mu$ mol/L). The absolute reticulocyte count was 416 G/L (25–102 G/L), the reticulocyte production index (RPI) was 8.5,

and erythroblasts were 303/100 leukocytes. These values were consistent with severe hemolysis. The DAT before the transfusion was negative (day -20), but the one after showed a weak anti-IgG and an anti-C3d positive result (day -5 before admission, performed in an outpatient control), the antibody elution was negative. The antibody screening test detected new anti-N and anti-Le(b) alloantibodies, along with previously known anti-Cw alloantibodies (confirmed by the Swiss Reference Laboratory for Immunohematology) (Table 1). At this point, the hemolysis was considered to be alloantibody-associated. The anti-N alloantibody very rarely causes hemolysis [21–23], but severe delayed hemolytic reaction due to anti-Le(b) alloantibodies have been described [24]. At hospital admission (day 0), two phenotype-matching PRBCs were administered. Two matched PRBCs had to be given on days +1 and +3, whereby a nationwide search for PRBC became necessary due to the antibody profile. An exchange transfusion could not take place due to the lack of compatible PRBCs (Table 1) [25].

During the transfusion therapy, an increase in hemolysis (Fig. 1) was observed. The fetal wellbeing was monitored, and no signs of fetal anemia or fetal distress were detected. Based on the clinical presentation, we suspected macrophage-mediated HHS activated by alloantibodies. This was supported by laboratory analyses by comparing current Hb values to ones from 4 months prior. HbS showed a decrease from 73.4% to 59.7%, HbF from 16.4% to 7.6% on day 2, with a low of 4.3% on day 16. Additionally, HbA decreased from 23.9% (day +1) to 11.4% (day +15). Prevalues unfortunately do not exist (Table 2). These values were concluded to be an indirect sign of HHS.

### Treatment of HHS

In order to avoid worsening symptoms, PRBC transfusion was ceased, and the patient was given immunoglobulin therapy (IVIG) with 1 g/kg body weight on day 10 and 2 g/kg body weight on day 16. In addition, the patient received methylprednisolone 1 g IV (once daily on days +10, +17, and +18), which was 15 mg/kg/d. Afterward, the treatment was continued with oral prednisolone 20 mg/day, and later increased to 40 mg/d for the remainder of the hospitalization. On day +33, the last dose of IVIG 2 g/kg per body weight was administered in preparation for a caesarean section (C-section). The patient received low-molecular-weight heparin (dalteparin), 5,000 IU of one subcutaneous injection daily as thromboprophylaxis. Additionally, a weekly dose of vitamin B12 and 10 mg of folic acid daily were also given to promote erythropoiesis. Throughout the hospitalization, the patient received oxygen and adequate hydration. The administration of eculizumab to stop complement-mediated hemolysis and the use of erythropoietin were discussed; however, this was determined to be unnecessary as the patient was stabilized.

### Pregnancy Outcome

At 34 weeks of gestation (day 35 of her hospitalization), a placental insufficiency was suspected due to reduced fetal growth velocity. Doppler ultrasound revealed an increased umbilical artery pulsatility index with signs of cerebral blood flow redistribution. Peak systolic velocity of the arteria

**Table 3.** Overview of published case reports related to a HHS

HHS case reports				
authors	title	year	published in	
Aragona and Kelly [37]	Hyperhemolysis in Sickle Cell Disease	2014	J Pediatric Hematol/Oncol, 36(1), 54–56. <a href="https://doi.org/10.1097/MPH.0b013e31828e529f">https://doi.org/10.1097/MPH.0b013e31828e529f</a>	
Chinchilla Langeber et al. [38]	When a Transfusion in an Emergency Service Is Not Really Urgent: Hyperhaemolysis Syndrome in a Child with Sickle Cell Disease	2018	BMJ Case Rep, 2018. <a href="https://doi.org/10.1136/bcr-2017-223209">https://doi.org/10.1136/bcr-2017-223209</a>	
Cullis et al. [35]	Post-Transfusion Hyperhaemolysis in a Patient with Sickle Cell Disease: Use of Steroids and Intravenous Immunoglobulin to Prevent Further Red Cell Destruction	1995	Vox Sanguinis, 69(4), 355–357. <a href="https://doi.org/10.1111/j.1423-0410.1995.tb00373.x">https://doi.org/10.1111/j.1423-0410.1995.tb00373.x</a>	
Eberly et al. [34]	Hyperhemolysis Syndrome without Underlying Hematologic Disease	2015	Case Rep Hematol, 2015, 1–3. <a href="https://doi.org/10.1155/2015/180526">https://doi.org/10.1155/2015/180526</a>	
Epstein and Hadley [39]	Successful Management of the Potentially Fatal Hyperhaemolysis Syndrome of Sickle Cell anaemia with a Regimen Including Bortezomib and Hemopure	2019	J Clin Pharmacy Therapeutics, 44(5), 815–818. <a href="https://doi.org/10.1111/jcpt.12998">https://doi.org/10.1111/jcpt.12998</a>	
Fuja et al. [40]	Hyperhemolysis in a Patient with Sickle Cell Disease and Recent SARS-CoV-2 Infection, with Complex Auto- and Alloantibody Work-Up, Successfully Treated with Tocilizumab	2022	Transfusion, 62(7), 1446–1451. <a href="https://doi.org/10.1111/trf.16932">https://doi.org/10.1111/trf.16932</a>	
Gouveia et al. [41]	Hyperhemolysis Syndrome in a Patient with Sickle Cell Anemia: Case Report	2015	Revista Brasileira de Hematologia e Hemoterapia, 37(4), 266–268. <a href="https://doi.org/10.1016/j.bbhh.2015.03.005">https://doi.org/10.1016/j.bbhh.2015.03.005</a>	
Gupta et al. [42]	Hyperhemolysis syndrome in a patient without a hemoglobinopathy, unresponsive to treatment with eculizumab	2015	Transfusion, 55(3), 623–628. <a href="https://doi.org/10.1111/trf.12876">https://doi.org/10.1111/trf.12876</a>	
Kalter et al. [17]	Hyperhemolysis Syndrome in a Patient with Sickle Cell Disease: A Case Report	2021	Clin Practice Cases Emergency Med, 5(1), 101–104. <a href="https://doi.org/10.5811/cpcem.2020.12.50349">https://doi.org/10.5811/cpcem.2020.12.50349</a>	
Karafin et al. [43]	A Fatal Case of Immune Hyperhemolysis with Bone Marrow Necrosis in a Patient with Sickle Cell Disease	2017	Hematolo Rep, 9(1), 8–11. <a href="https://doi.org/10.4081/hr.2017.6934">https://doi.org/10.4081/hr.2017.6934</a>	
Kasinathan and Sathar [44]	Post-Transfusion Hyperhemolysis Syndrome in a Patient with Beta Thalassemia Major	2021	Clin Case Rep, 9(6), 10–13. <a href="https://doi.org/10.1002/ccr3.4226">https://doi.org/10.1002/ccr3.4226</a>	
Lu et al. [45]	Hyperhemolysis Syndrome: A Relative Contraindication for Transfusion	2008	J Hospital Med, 3(1), 78–80. <a href="https://doi.org/10.1002/jhm.257">https://doi.org/10.1002/jhm.257</a>	
Menakuru et al. [40]	Acute Hyperhemolysis Syndrome in a Patient with Known Sickle Cell Anemia Refractory to Steroids and IVIG Treated with Tocilizumab and Erythropoietin: A Case Report and Review of Literature	2022	Hematol Rep, 14(3), 235–239. <a href="https://doi.org/10.3390/hematolrep14030032">https://doi.org/10.3390/hematolrep14030032</a>	
Narbey et al. [33]	Incidence and Predictive Score for Delayed Hemolytic Transfusion Reaction in Adult Patients with Sickle Cell Disease		Am J Hematol. 2017;92:13401348.doi:10.1002/ajh.24908	
Rehman et al. [46]	Recurrent Hyperhemolysis Syndrome in Sickle Cell Disease	2021	Cureus, 13(5), 13–15. <a href="https://doi.org/10.7759/cureus.14991">https://doi.org/10.7759/cureus.14991</a>	
Santos et al. [47]	Hyperhemolysis Syndrome in Patients with Sickle Cell Anemia: Report of Three Cases	2015	Transfusion, 55(6), 1394–1398. <a href="https://doi.org/10.1111/trf.12993">https://doi.org/10.1111/trf.12993</a>	

**Table 3** (continued)

HHS case reports				
authors	title	year	published in	
Senanayake et al. [48]	Hyperhaemolysis Syndrome in Haemoglobin E/Beta Thalassaemia Responding to Cyclophosphamide Therapy	2008	Ceylon Med J, 53(4), 134–135. <a href="https://doi.org/10.4038/cmj.v53i4.283">https://doi.org/10.4038/cmj.v53i4.283</a>	
Shankar et al. [49]	Hyperhemolysis Syndrome in a Patient With Sickle Cell Disease and Acute Chest Syndrome	2021	Cureus, 13(1), 1–5. <a href="https://doi.org/10.7759/cureus.13017">https://doi.org/10.7759/cureus.13017</a>	
Sivapalaratnam et al. [50]	Treatment of Post-Transfusion Hyperhaemolysis Syndrome in Sickle Cell Disease with the Anti-IL6R Humanised Monoclonal Antibody Tocilizumab	2019	British J Haematology, 186(6), e212–e214. <a href="https://doi.org/10.1111/bjh.16103">https://doi.org/10.1111/bjh.16103</a>	
Sokolova et al. [51]	A Case of Hyperhemolytic Anemia	2016	J Hematology, 5(1), 38–40. <a href="https://doi.org/10.14740/jh266e">https://doi.org/10.14740/jh266e</a>	
Sweidan et al. [10]	Hyperhemolysis Syndrome in SCD Patient: Reminder of a Rare but Life-Threatening Complication of Blood Transfusion	2021	Blood, 138(Supplement 1), 4282–4282. <a href="https://doi.org/10.1182/blood-2021-152788">https://doi.org/10.1182/blood-2021-152788</a>	
Treleaven et al. [52]	Hyperhaemolysis Syndrome in a Patient with Myelofibrosis	2004	Hematology, 9(2), 147–149. <a href="https://doi.org/10.1080/1024533042000205478">https://doi.org/10.1080/1024533042000205478</a>	
Uhlmann et al. [25]	Successful Treatment of Recurrent Hyperhemolysis Syndrome with Immunosuppression and Plasma-to-Red Blood Cell Exchange Transfusion	2014	Transfusion, 54(2), 384–388. <a href="https://doi.org/10.1111/trf.12258">https://doi.org/10.1111/trf.12258</a>	
Vagace et al. [53]	Hyperhaemolysis Syndrome Responsive to Splenectomy in a Patient with δβ-Thalassaemia: A Discussion on Underlying Mechanisms	2014	Blood Transfusion, 12(1), 127–129. <a href="https://doi.org/10.2450/2013.0059-13">https://doi.org/10.2450/2013.0059-13</a>	
Vlachaki et al. [54]	Successful Outcome of Hyperhemolysis in Sickle Cell Disease following Multiple Lines of Treatment: The Role of Complement Inhibition	2018	Hemoglobin, 42(5–6), 339–341. <a href="https://doi.org/10.1080/03630269.2018.1540353">https://doi.org/10.1080/03630269.2018.1540353</a>	
Win et al. [18]	Hyperhemolysis Syndrome in Sickle Cell Disease: Case Report (Recurrent Episode) and Literature Review	2008	Transfusion, 48(6), 1231–1238. <a href="https://doi.org/10.1111/j.1537-2995.2008.01693.x">https://doi.org/10.1111/j.1537-2995.2008.01693.x</a>	
HHS case reports related to pregnancy				
authors	title	year	published in	treatment of HHS described
Asnawi et al. [8]	Fatal Delayed Haemolytic Transfusion Reaction and Hyperhaemolysis Syndrome in a Pregnant Woman with Sickle Cell Anaemia	2016	Indian J Hematology Blood Transfusion, 32(June), 251–253. <a href="https://doi.org/10.1007/s12288-014-0495-9">https://doi.org/10.1007/s12288-014-0495-9</a>	Blood exchange
Mechery et al. [55]	Hyperhemolysis Syndrome Complicating Pregnancy in Homozygous δβ-Thalassemia	2012	Hemoglobin, 36(2), 183–185. <a href="https://doi.org/10.3109/03630269.2011.649150">https://doi.org/10.3109/03630269.2011.649150</a>	Corticosteroids, IVIG, cyclosporin
Vasantha mohan et al. [56]	Peripartum hyperhemolysis Prophylaxis and Management in Sickle Cell Disease: A Case Report and Narrative Review	2020	Transfusion, 60(10), 2448–2455. <a href="https://doi.org/10.1111/trf.16003">https://doi.org/10.1111/trf.16003</a>	Prophylaxis corticosteroids, IVIG postpartum rituximab
Wu et al. [9]	A Case of Hyperhaemolysis Syndrome in a Pregnant Chinese Woman with β-Thalassemia during Perinatal Transfusion	2021	Transfus Med, 31(1), 24–29. <a href="https://doi.org/10.1111/tme.12748">https://doi.org/10.1111/tme.12748</a>	Corticosteroids, IVIG, rituximab, blood exchange

**Table 3** (continued)

HHS case reports related to pregnancy				
authors	title	year	published in	treatment of HHS described
Bezirgiannidou et al. [57]	Hyperhemolytic Syndrome Complicating a Delayed Hemolytic Transfusion Reaction due to Anti-P1 Alloimmunization, in a Pregnant Woman with HbO-Arab/ $\beta$ -Thalassemia	2016	Mediterr J Hematol Infect Dis. 2016; 8(1): e2016053 Published online 2016 Oct 18. doi: 10.4084/MJHID.2016.053	Corticosteroids, IVIG
Unnikrishnan et al. [58]	Anti-N and anti-Doa Immunoglobulin G Alloantibody-Mediated Delayed Hemolytic Transfusion Reaction with Hyperhemolysis in Sickle Cell Disease Treated with Eculizumab and HBOC-201: Case Report and Review of the Literature	2019	J AABB Transfusion, Volume59, Issue6, June 2019, Pages 1907-1910	Corticosteroids, eculizumab

The table shows an overview of the case reports involving HHS, as well as specifically case reports with pregnant women and their therapy regimen.

cerebri media was below 1.5 MoM, therefore excluding severe fetal anemia [24, 25]. These findings led to the decision to perform a C-section at 34 weeks gestation. On the day of the C-section, the patient had a Hb of 56 g/L and received one compatible PRBC without immunomodulatory therapy. The C-section was performed without complications. A healthy boy was born and transferred to the neonatology unit. The child showed no signs of hemolysis and his DAT was negative. The patient was discharged 45 days after admission; she had a Hb of 63 g/L and attenuated signs of hemolysis. Currently, the patient and her child, who is already 4 years old, are doing well. She has not received any further PRBCs and has had no further episodes of hyperhemolysis.

## Discussion

HHS was diagnosed in a pregnant patient with compound-heterozygous SCD/ $\beta^0$ -thalassemia due to symptomatic hemolysis 3 weeks after transfusion of a PRBC and with formation of new erythrocyte alloantibodies [5, 12, 20, 26]. Due to the greater presence of hemolysis due to the underlying hemoglobinopathy in patients affected with HHS, it is frequently misdiagnosed, followed by an increased risk of potentially fatal complications occurring due to a delayed diagnosis [17]. Especially in patients with hemoglobinopathies and a history of transfusions, HHS should be considered, when presenting with posttransfusion hemolysis.

One potential strategy to avoid developing HHS could be the consistent implementation of extended antigen typing of blood products, as well as the determination of high-throughput genotyping [20, 27]. This could prevent the formation of alloantibodies against high-frequency antigens, particularly by the Rh system [28], and in the course, lowering the risk of HHS [29–31]. However, this would not eliminate the risk completely [11]. Furthermore, the prerequisite would be a sufficient donor pool [32].

Currently, there are no evidenced-based treatment guidelines for HHS. When HHS occurs, it is imperative to prevent further hemolysis [13, 16, 20, 33, 34], especially when this occurs in pregnant women [8, 9], as the resulting anemia increases both maternal and fetal morbidity and mortality even in mild cases [35, 36]. Of the published cases (Table 3) that reported HHS, there appeared to be a higher prevalence occurring in females along with a majority of cases being associated with SCD. Unfortunately, there are very few publications about pregnant women that could be used as a guidance (Table 3) [8, 9, 29]. Therapy schemes cannot be derived from them.

Since hemolysis is exacerbated by continuous transfusions, as this further aggravates the immunological reaction [13, 16, 30, 33, 34], the first step that should be taken, is to stop transfusion therapy, as much as the patient's condition allows. Despite the lack of guidelines, most publications report the use of steroids and immunoglobulins (IVIG) to stop the

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immunologically induced hemolysis (see Table 3) showing a general acceptance of the treatment protocol [59].

Complement inhibitors (anti-C5 monoclonal antibody) such as eculizumab have been used in a few HHS cases, where it seemed promising in some, particularly when there was an activation of the complement pathway. Anti-C5 dosing must be individualized between a one-time dose of 900 mg i.v. and a second dose on day 7 if hemolysis is still ongoing [42, 47, 48]. However, there are no prospective studies that confirm the effectiveness and lack of response has also been reported [60]. Furthermore, there are increasing reports of successful treatment with anti-IL-6 receptor monoclonal antibodies such as tocilizumab, particularly in patients with SCD, as they have higher levels of circulating cytokines such as IL-1, TNF- $\alpha$ , and IL-6 [50, 61]. Although there are promising case reports, further study is needed to verify the efficacy [51, 52].

Cyclophosphamide and rituximab [53, 55] have also been used, sometimes in combination with IVIG, if there is an inadequate response to steroid therapy or as a steroid-sparing agent. The use of rituximab has also been reported in some cases, despite its low efficacy [60].

A main benefit of rituximab for pregnant women is that transplacental transfer of IgG is limited, so that B-cell depletion in the fetus is mainly observed when this drug is used during the last trimesters [44, 57]. A number of measures to promote (maternal) erythropoiesis, using adjuvant therapy with vitamin B12, folic acid, and eventually erythropoietin can be beneficial [56].

The critical nature of this case demonstrates the need for interdisciplinary teamwork between hematologists, transfusion medicine specialists, and obstetricians in order to more accurately and more rapidly reach a conclusive diagnosis and begin treatment. We would like to dedicate a special mention to the national and international blood bank network, which enabled us to quickly receive compatible blood products and rapidly perform pheno- and genotyping.

## Conclusion

HHS is a rare cause of hemolysis. A diagnosis of HHS is often delayed and leads to severe complications. Transfusions, hemoglobinopathies, and multiple alloimmunizations are the main risk factors for the development of HHS. In many cases, despite the

severe anemia, ceasing transfusions and implementing non-transfusion strategies is the only viable option to manage HHS. HHS in pregnant women is particularly complex and requires a multidisciplinary team to ensure the health of the mother and unborn child.

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## Statement of Ethics

Written informed consent was obtained from the patient for publication of this case report and any accompanying images. Ethical approval is not required for this study in accordance with local or national guidelines.

## Conflict of Interest Statement

The authors declare no conflicts of interest.

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## Author Contributions

Anke Rihsling, Helena Simeunovic, and Alicia Rovó contributed to conception of the manuscript. Alicia Rovó, Helena Simeunovic, and Martin Müller treated the patient and provided clinical information. Anke Rihsling, Sergio Sanchez, Alicia Rovó, Luigi Raio, Michael Daskalakis, and Behrouz Mansouri Teleghani contributed to literature review. Christine Henny and Sofia Crottet Lejon performed and interpreted the immunohematology results. All the co-authors participated in the edition of the manuscript and approved the final version.

## Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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