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"Don't add fuel to the fire"- Hyperhemolysis Syndrome in a pregnant woman with compound Sickle cell disease/ß^0-thalassemia - Case report and review of the literature"

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Abstract

Hyperhemolysis Syndrome (HHS) is a rare and severe post-transfusion complication characterized by the destruction of both recipient and donor red blood cells (RBC). 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/ß-^{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.

Introduction

Sickle cell disease (SCD) is a hemoglobinopathy due to a point mutation in the ß-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 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][8][9][10], in which both recipient and donor red blood cells are destroyed by intravascular hemolysis. In HHS, the HbA/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 (LDH) concentrations. Likewise, a relative low count of reticulocytes is common. [14] In rare cases, bone marrow progenitor cells can also be damaged, affecting red blood cell production, leading to severe anemia. The direct antiglobulin test (DAT) is often negative, but in some cases, it can show weakly positive IgG and C3d, and new alloantibodies are often also present. [12][13][14][15][16] The clinical presentation varies from fever, 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][19][20] The main known predisposing risk factors for HHS are transfusion and hemoglobinopathies but certain factors such as multiple alloimmunizations [11][15][20][21], non-B blood type and compound ßß^0-thalassaemia have been theorized to play a role exacerbating the risk of developing HHS. [14][20] A genetic predisposition has also been proposed as a risk factor, as not every SCD patient develops HHS. [13]

We report a case of a pregnant patient with compound SCD/β^0-thalassaemia 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. [23]

Case Report

Medical History, Diagnostics and Transfusion management

We present a 36-year-old female patient, who was diagnosed with SCD/β^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 hemoglobin (Hb) values were around 80 g/L (121-154g/L). At the age of 22, she received transfusions on two occasions, the transfusion history prior to this is unknown (*table 1*).

At 26 weeks 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 *figure 1*,day -20 before admission). The pheno-/genotype (genotyping was performed on day 3 of the hospitalization) of the patient is: *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 LDH of 1037U/L (<480U/L) *(figure 1)*, undetectable haptoglobin (<0.10g/L) and a normal bilirubin of 10umol/L (<17umol/L). The absolute reticulocyte count was 416G/L (25-102G/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 [24][25][26], but severe delayed hemolytic reaction due to anti-Le(b) alloantibodies have been described. [27] 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*). [28]
During the transfusion therapy, an increase in hemolysis (*Figure 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 1g/kg body weight on day 10 and 2g/kg body weight on day 16. In addition. The patient received methylprednisolone 1g IV (once daily on days +10, +17 and +18), which was 15mg/kg/d. Afterwards the treatment was continued with oral prednisolone 20 mg/day, and later increased to 40mg/d for the remainder of the hospitalization. On day +33, the last dose of IVIG 2g/kg per body weight was administered in preparation for a caesarean section (C-section). The patient received low-molecular-weight heparin (LMWH/Dalteparin), 5000 IU one subcutaneous (SC) 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 was discussed; however, this was determined to be unnecessary as the patient was stabilized.

Pregnancy outcome

At 34 weeks 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 cerebri media was below 1.5 MoM, therefore excluding severe fetal anemia [28] 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 56g/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 no further episodes of hyperhemolysis.

Discussion

HHS was diagnosed in a pregnant patient with compound-heterozygous sickle cell disease/β^0-thalassemia due to symptomatic hemolysis three weeks after transfusion of a PRBC and with formation of new erythrocyte alloantibodies.[5][14][20][21] 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 post-transfusion 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] This could prevent the formation of alloantibodies against high-frequency antigens, particularly by the Rh system [30], and in the course, lowering the

risk of HHS. [31][32][33] However, this would not eliminate the risk completely [11] Furthermore, the prerequisite would be a sufficiently donor pool. [34]
Currently, there are no evidenced based treatment guidelines for HHS. When HHS occurs, it is imperative to prevent further hemolysis [14][16][20][35][36], 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. [37][38] 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][31] Therapy schemes cannot be derived from them.
Since hemolysis is exacerbated by continuous transfusions, as this further aggravates the immunological reaction [14][16][35][36][39], 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 immunologically induced hemolysis (see *table 3*) showing a general acceptance of the treatment protocol. [40]
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 900mg i.v. and a second dose on day 7 if hemolysis is still ongoing. [41][42][43] However, there are no prospective studies that confirm the effectiveness and lack of response has also been reported. [44] 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-α and IL-6. [45][46] Although there are promising case reports, further study is needed to verify the efficacy. [47]
Cyclophosphamide and rituximab [49][50] 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. [44]
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. [51][52]
A number of measures to promote (maternal) erythropoiesis, using adjuvant therapy with vitamin B12, folic acid, and eventually erythropoietin can be beneficial. [52]
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.

Conflicts of Interest
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 analysed during this study are included in this article. Further enquiries can be directed to the corresponding author.

References

1 Meremikwu M. Sickle cell disease. *Clin Evid (Online)*. 2006;(15):45-59. doi:10.1056/NEJMra1510865

2 Darbari DS, Sheehan VA, Ballas SK. The vaso-occlusive pain crisis in sickle cell disease: Definition, pathophysiology, and management. *Eur J Haematol*. 2020;105(3):237-246. doi:10.1111/ejh.13430

3 Ware RE, de Montalembert M, Tshilolo L, Abboud MR. Sickle cell disease. *Lancet*. 2017;390(10091):311-323. doi:10.1016/S0140-6736(17)30193-9

4 Chou ST, Alsawas M, Fasano RM, et al. American society of hematology 2020 guidelines for sickle cell disease: Transfusion support. *Blood Adv*. 2020;4(2):327-355. doi:10.1182/BLOODADVANCES.2019001143

5 Han H, Hensch L, Tubman VN. Indications for transfusion in the management of sickle cell disease. *Hematol (United States)*. 2021;2021(1):696-703. doi:10.1182/hematology.2021000307

6 Linder GE, Chou ST. Red cell transfusion and alloimmunization in sickle cell disease. *Haematologica*. 2021;106(7):1805-1815. doi:10.3324/haematol.2020.270546

7 Madu AJ, Ugwu AO, Efobi C. Hyperhaemolytic syndrome in sickle cell disease: Clearing the cobwebs. *Med Princ Pract*. 2021;30(3):236-243. doi:10.1159/000512945

8 Asnawi AWA, Sathar J, Mohamed R, et al. Fatal Delayed Haemolytic Transfusion Reaction and Hyperhaemolysis Syndrome in a Pregnant Woman with Sickle Cell Anaemia. *Indian J Hematol Blood Transfus*. 2016;32(June):251-253. doi:10.1007/s12288-014-0495-9

9 Wu Y, Ji Y, Dai B, et al. A case of hyperhaemolysis syndrome in a pregnant Chinese woman with β-thalassemia during perinatal transfusion. *Transfus Med*. 2021;31(1):24-29. doi:10.1111/tme.12748

10 Sweidan A, Vuyyala S, Xie P, Alhyari M, Dabak VS, Z. Otrock ZK, Hyperhemolysis Syndrome in SCD Patient: Reminder of a Rare but Life-Threatening Complication of Blood Transfusion, *Blood*, vol. 138, no. Supplement 1, pp. 4282–4282, 2021, doi: 10.1182/blood-2021-152788

11 Pirenne F, Yazdanbakhsh K, How I safely transfuse patients with sickle-cell disease and manage delayed hemolytic transfusion reactions, *Blood*, vol. 131, no. 25, pp. 2773–2781, 2018, doi: 10.1182/blood-2018-02-785964.

12 Banks M, Shikle J, Hyperhemolysis Syndrome in Patients With Sickle Cell Disease, *Arch Pathol Lab Med* (2018) 142 (11): 1425–1427. https://doi.org/10.5858/arpa.2017-0251-RS

13 Omer SA, Alaesh JS, Algadeeb KB, Delayed hemolytic transfusion reaction in a patient with sickle cell disease: Case report, *Int. Med. Case Rep. J.*, vol. 13, pp. 307–311, 2020, doi: 10.2147/IMCRJ.S257036.

14 Merrill SA, Brodsky RA, Lanzkron SM, Naik R, A case-control analysis of hyperhemolysis syndrome in adults and laboratory correlates of complement involvement, *Transfusion*, vol. 59, no. 10, pp. 3129–3139, 2019, doi: 10.1111/trf.15445.

15 Petz LD, Calhoun L, Shulman IA, Johnson C, Herron RM. The sickle cell hemolytic transfusion reaction syndrome. *Transfusion*. 1997;37(4):382-392. doi:10.1046/j.1537-2995.1997.37497265338.x

16 Davey R, Gustafson M, Holland P, Accelerated immune red cell destruction in the absence of serologically detectable alloantibodies, *Transfusion*, vol. 20, no. 3, pp. 348–353, 1980, doi: 10.1046/j.1537-2995.1980.20380214905.x.

17 Kalter J, Gupta R, Greenberg M, Miller A, Allen J. Hyperhemolysis Syndrome in a Patient with Sickle Cell Disease: A Case Report. *Clin Pract Cases Emerg Med*. 2021;5(1):101-104. doi:10.5811/cpcem.2020.12.50349

18 Win N, New H, Lee E, De La Fuente J, Hyperhemolysis syndrome in sickle cell disease: Case report (recurrent episode) and literature review, *Transfusion*, vol. 48, no. 6, pp. 1231–1238, 2008, doi: 10.1111/j.1537-2995.2008.01693.x.

19 Roumenina LT, Bartolucci P, Pirenne F. The role of Complement in Post-Transfusion Hemolysis and Hyperhemolysis Reaction. *Transfus Med Rev*. 2019;33(4):225-230. doi:10.1016/j.tmrv.2019.09.007

20 Danaee A, Inusa B, Howard J, Robinson S. Hyperhemolysis in Patients With Hemoglobinopathies: A Single-Center Experience and Review of the Literature. *Transfus Med Rev*. 2015;29(4):220-230. doi:10.1016/j.tmrv.2015.06.001

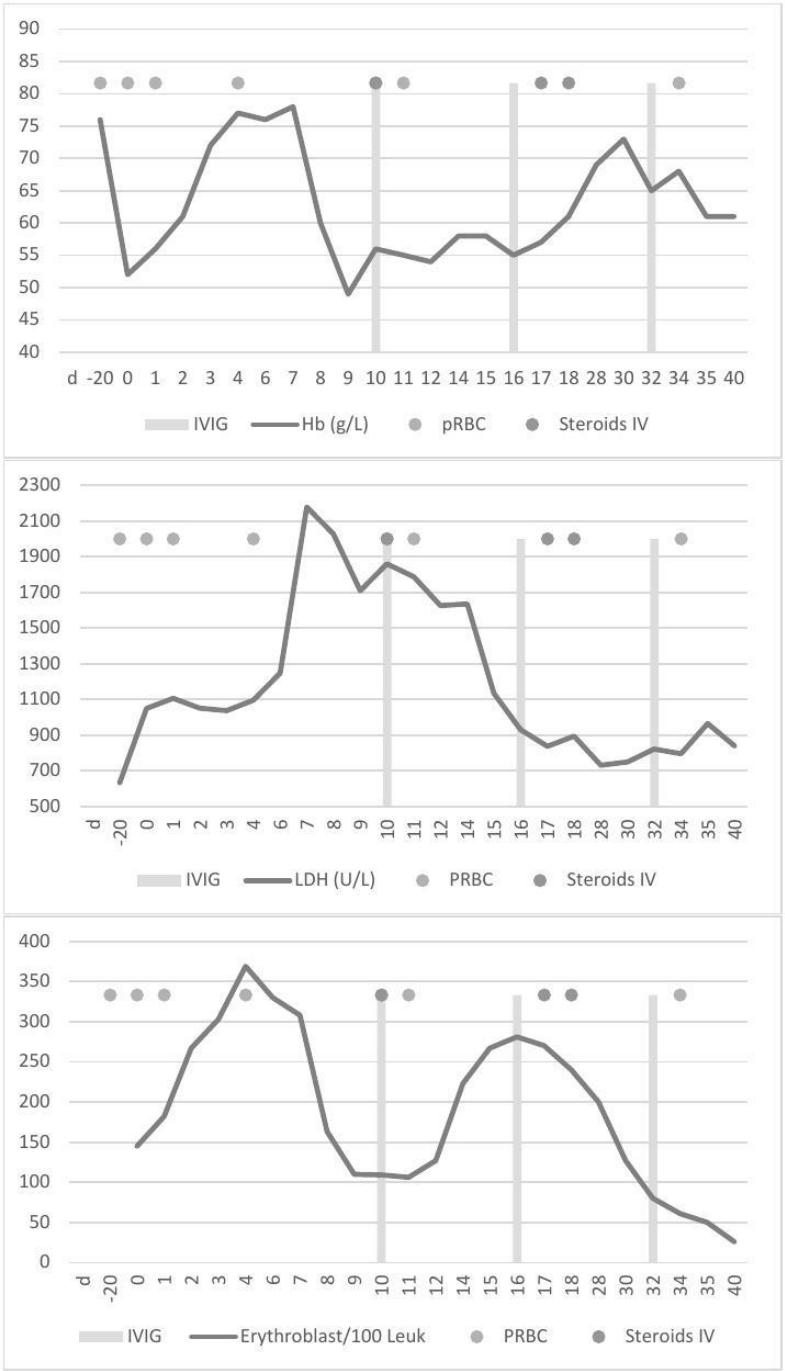
21 Thein SL, Pirenne F, Fasano RM, et al. Hemolytic transfusion reactions in sickle cell disease: Underappreciated and potentially fatal. *Haematologica*. 2020;105(3):539-544. doi:10.3324/haematol.2019.224709

22 Mwesigwa S, Moulds JM, Chen A, Flanagan J, Sheehan VA, George A, Hanchard NA. Whole-exome sequencing of sickle cell disease patients with hyperhemolysis syndrome suggests a role for rare variation in disease predisposition. *Transfusion*. 2018 Mar;58(3):726-735. doi: 10.1111/trf.14431.
23 Crottet SL, Song Y, Jutzi M. Der schwierige Fall : Bereitstellung antigen- kompatibler Erythrozytenkonzentrate bei einer schwangeren Sichelzellpatientin mit multiplen Antikörpern. 2017;(4):10-11.
24 Yoell JH, Immune Anti-N Agglutinin in Human Serum : Report of Apparent Associated Hemolytic Reaction. *Transfusion*, 6(6), 592–593. doi:10.1111/j.1537-2995.1966.tb04785.x
25 Reyes M A, Illoh O C, Hyperhemolytic transfusion reaction attributable to anti-Fy3 in a patient with sickle cell disease, *Immunohematology*. 2008;24(2):45-51.
26 Unnikrishnan, A., Pelletier, J.P.R., Bari, S., Zumberg, M., Shahmohamadi, A., Spiess, B.D., Michael, MJ., Harris, N., Harrell, D. and Mandernach, M.W. (2019). Anti-N and anti-Do^{a} 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. *Transfusion*, 2019, Jun;56(6): 1907-1910. doi:10.1111/trf.15198
27 Weir AB III, Woods LL, Chesney C, Neitzer G, Delayed Hemolytic Transfusion Reaction Caused by Anti-LebH Antibody, *Vox Sanguinis*, First published: August 1987 https://doi.org/10.1111/j.1423-0410.1987.tb04928.xCitations: 13
28 Uhlmann EJ, Shenoy S, Goodnough LT. Successful treatment of recurrent hyperhemolysis syndrome with immunosuppression and plasma-to-red blood cell exchange transfusion. *Transfusion*. 2014;54(2):384-388. doi:10.1111/trf.12258
29 Mari G. Noninvasive Diagnosis by Doppler Ultrasonography of Fetal Anemia Due to Maternal Red-Cell Alloimmunization. *Obstet Gynecol Surv*. 2000;55(6):341-342. doi:10.1097/00006254-200006000-00005
30 The Swiss Transfusion Medicine, Association (SVTM) and Swiss Transfusion SRC (B-CH) for healthcare professionals, and laboratories and medical institutions on immunohaematological and molecular testing of patient blood samples, Laboratory Testing of Patient Samples in Transfusion Medicine, V11.pp. 1–63, 2022.
31 Tamagne M, Pakdaman S, Bartolucci P, et al. Whole-blood phenotyping to assess alloimmunization status in transfused sickle cell disease patients. *Blood Adv*. 2021;5(5):1278-1282. doi:10.1182/bloodadvances.2020003537
32 Noizat-Pirenne F, Tournamille C, Relevance of RH variants in transfusion of sickle cell patients, *Transfus. Clin. Biol.*, vol. 18, no. 5–6, pp. 527–535, 2011, doi: 10.1016/j.tracli.2011.09.001.
33 Chou S, Jackson T, Vege S, Smith-Whitley K, Friedman DF, Westhoff CM. High prevalence of red blood cell alloimmunization in sickle cell disease despite transfusion from Rh-matched minority donors. Blood 2013;122:1062–71.
34 Chou ST, Evans P, Vege S, et al. RH genotype matching for transfusion support in sickle cell disease. *Blood*. 2018;132(11):1198-1207. doi:10.1182/blood-2018-05-851360
35 Narbey D, Habibi A, Chadebech P, Mekontso-Dessap A, Khellaf M; Lelièvre, JD, Godeau B, Michel M; Galactéros F, Djoudi R, Bartolucci P; Pirenne F, Incidence and predictive score for delayed hemolytic transfusion reaction in adult patients with sickle cell disease. *Am J Hematol.* 2017;92:1340–1348.doi:10.1002/ajh.24908
36 Cullis JO, Win N, Dudley JM, Kaye T. Post-Transfusion Hyperhaemolysis in a Patient with Sickle Cell Disease: Use of Steroids and Intravenous Immunoglobulin to Prevent Further Red Cell Destruction. *Vox Sang*. 1995;69(4):355-357. doi:10.1111/j.1423-0410.1995.tb00373.x
37 El Guindi W *et al.*, Anémies maternelles sévères et issues de grossesse, *J. Gynécologie Obs. Biol. la Reprod.*, vol. 33, no. 6, pp. 506–509, 2004, doi: 10.1016/s0368-2315(04)96563-5.
38 Smith C, Teng F, Branch E, Chu S, Joseph KS. Maternal and Perinatal Morbidity and Mortality Associated with Anemia in Pregnancy. *Obstet Gynecol*. 2019;134(6):1234-1244. doi:10.1097/AOG.0000000000003557
39 Noizat-Pirenne F, Tournamille C, Relevance of RH variants in transfusion of sickle cell patients, *Transfus. Clin. Biol.*, vol. 18, no. 5–6, pp. 527–535, 2011, doi: 10.1016/j.tracli.2011.09.001.
40 Chonat S, Connie M. Arthur CM, Zerra PE, Maier CL, Jajosky RP, Yee M EM, Miller MJ, Josephson CD, Roback JD, Fasano R, Stowell SR, Challenges in preventing and treating hemolytic complicationsassociated with red blood cell transfusion/Défis dans la prévention et le traitement des complications hémolytiques associéesà la transfusion de globules rouges, *Transfusion Clinique et Biologique*, Volume 26, Issue 2, May 2019, Pages 130-134

41 Pirenne F, Bartoluccib P, Habibib A, Management of delayed hemolytic transfusion reaction in sickle cell disease: Prevention, diagnosis, treatment/Hémolyse post transfusionnelle du patient drépanocytaire : prévention, diagnostic, traitement, *Transfusion Clinique et Biologique, 2017,* http://dx.doi.org/10.1016/j.tracli.2017.05.016
42 Vlachaki E, Gavriilaki E, Kafantari K, et al. Successful Outcome of Hyperhemolysis in Sickle Cell Disease following Multiple Lines of Treatment: The Role of Complement Inhibition. *Hemoglobin*. 2018;42(5-6):339-341. doi:10.1080/03630269.2018.1540353
43 Chonat S, Quarmyne M-O, Stowell SR. Contribution of alternative complement pathway to delayed hemolytic transfusion reaction in sickle cell disease. *Haematologica*. 103(10):haematol.2018.194670. doi:10.3324/haematol.2018.194670
44 NHSE. Clinical Commissioning Policy; Rituximab and eculizumab for the prevention and management of delayed haemolytic transfusion reactions and hyperhaemolysis in patients with haemoglobinopathies. Published online 2020:1-13. https://www.england.nhs.uk/wp-content/uploads/2020/09/1821_Rituximab_Eculizumab_Clinical_Commissioning_Policy.pdf
45 Menakuru SR, Priscu A, Dhillon V, Salih A. 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. *Hematol Rep*. 2022;14(3):235-239. doi:10.3390/hematolrep14030032
46 Fuja C, Kothary V, Carll TC, Singh S, Mansfield P, Wool GD. 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. *Transfusion*. 2022;62(7):1446-1451. doi:10.1111/trf.16932
47 Meenan J, Hall R, Badle S, Chatterjee B, Win N, Tsitsikas DA. Tocilizumab in the management of posttransfusion hyperhemolysis syndrome in sickle cell disease: The experience so far. *Transfusion*. 2022;62(3):546-550. doi:10.1111/trf.16805
48 Lee LE, Beeler BW, Graham BC, Cap AP, Win N, Chen F.**,** Posttransfusion hyperhemolysis is arrested by targeting macrophage activation with novel use of Tocilizumab. *Transfusion*. 2020 Jan;60(1):30-35. doi: 10.1111/trf.15562. Epub 2019 Oct 23.
49 Bachmeyer C, Maury J, Parrot A, Bachir D, Stankovic K, Girot R, Lionnet F. Rituximab as an effective treatment of hyperhemolysis syndrome in sickle cell anemia. *Am J Hematol*. . 2010 Jan;85(1):91-2. doi: 10.1002/ ajh.21578.
50 Noizat-Pirenne F, Bachir D, Chadebech P, et al. Rituximab for prevention of delayed hemolytic transfusion reaction in sickle cell disease. *Haematologica*. 2007;92(12):132-135. doi:10.3324/haematol.12074
51 Das G, Damotte V, Gelfand J M,Bevan C, Cree B A C, Do L, Green A J, Hauser S L, Riley Bove R; Rituximab before and during pregnancy A systematic review, and a case series in MS and NMOSD, *Neurol Neuroimmunol Neuroinflamm* 2018;5:e453. doi:10.1212/NXI.0000000000000453
52 Vasanthamohan L, Choo S, Marshall T, et al. Peripartum hyperhemolysis prophylaxis and management in sickle cell disease: A case report and narrative review. *Transfusion*. 2020;60(10):2448-2455. doi:10.1111/trf.16003
53 Aragona, E., & Kelly, M. J., hyperhemolysis in sickle cell disease, 2014, *Journal of Pediatric Hematology/Oncology*,*36*(1), 54–56. https://doi.org/10.1097/MPH.0b013e31828e529f
54 Chinchilla Langeber, S., Osuna Marco, M. P., Benedit, M., & Cervera Bravo, Á., When a transfusion in an emergency service is not really urgent: Hyperhaemolysis syndrome in a child with sickle cell disease, 2018, *BMJ Case Reports*, *2018*. https://doi.org/10.1136/bcr-2017-223209
55 Eberly, L. A., Osman, D., & Collins, N. P., Hyperhemolysis Syndrome without Underlying Hematologic Disease, 2015, *Vox Sanguinis*, *69*(4), 355–357. https://doi.org/10.1111/j.1423-0410.1995.tb00373.x
56 Epstein, S. S., & Hadley, T. J., Successful management of the potentially fatal hyperhaemolysis syndrome of sickle cell anaemia with a regimen including bortezomib and Hemopure, 2019, *Journal of Clinical Pharmacy and Therapeutics*, *44*(5), 815–818. https://doi.org/10.1111/jcpt.12998
57 Gouveia, M. E., Soares, N. B., Santoro, M. S. A., & de Azevedo, F. C. M., Hyperhemolysis syndrome in a patient with sickle cell anemia: Case report, 2015, *Revista Brasileira de Hematologia e Hemoterapia*, *37*(4), 266–268. https://doi.org/10.1016/j.bjhh.2015.03.005
58 Gupta, S., Fenves, A., Nance, S. T., Sykes, D. B., & Dzik, W., Hyperhemolysis syndrome in a patient without a hemoglobinopathy, unresponsive to treatment with eculizumab, 2015, *Transfusion*, *55*(3), 623–628. https://doi.org/10.1111/trf.12876

59 Karatin, M. S., Singavi, A., Johnson, S. T., & Field, J. J., A fatal case of immune hyperhemolysis with bone marrow necrosis in a patient with sickle cell disease, 2017, *Hematology Reports*, *9*(1), 8–11. https://doi.org/10.4081/hr.2017.6934
60 Kasinathan, G., & Sathar, J., Post-transfusion hyperhemolysis syndrome in a patient with beta thalassemia major, 2021, *Clinical Case Reports*, *9*(6), 10–13. https://doi.org/10.1002/ccr3.4226
61 Lu, R. P., Clark, P., & Mintz, P. D., Hyperhemolysis sydrome: A relative contraindication for transfusion, 2008, *Journal of Hospital Medicine*, *3*(1), 78–80. https://doi.org/10.1002/jhm.257
62 Rehman, R., Saadat, S. B., Tran, D. H., Constantinescu, S., & Qamruzzaman, Y., Recurrent Hyperhemolysis Syndrome in Sickle Cell Disease, 2021, *Cureus*, *13*(5), 13–15. https://doi.org/10.7759/cureus.14991
63 Santos, B., Portugal, R., Nogueira, C., & Loureiro, M, Hyperhemolysis syndrome in patients with sickle cell anemia: Report of three cases, 2015, *Transfusion*, *55*(6), 1394–1398. https://doi.org/10.1111/trf.12993
64 Senanayake, M. P., Kuruppu, K. K., Sumanasena, S. P., & Lamabadusuriya, S. P., Hyperhaemolysis syndrome in haemoglobin E / beta thalassaemia responding to cyclophosphamide therapy, 2008, *The Ceylon Medical Journal*, *53*(4), 134–135. https://doi.org/10.4038/cmj.v53i4.283
65 Shankar, K., Shah, D., Huffman, D. L., Peterson, C., & Bhagavatula, R., Hyperhemolysis Syndrome in a Patient With Sickle Cell Disease and Acute Chest Syndrome, 2021, *Cureus*, *13*(1),1-5 https://doi.org/10.7759/cureus. 13017
66 Sivapalaratnam, S., Linpower, L., Sirigireddy, B., Agapidou, A., Jain, S., Win, N., & Tsitsikas, D. A., Treatment of post-transfusion hyperhaemolysis syndrome in Sickle Cell Disease with the anti-IL6R humanised monoclonal antibody Tocilizumab, 2019, *British Journal of Haematology*, *186*(6), e212–e214. https://doi.org/10.1111/bjh.16103
67 Sokolova, A., & Darabi, K, A Case of Hyperhemolytic Anemia, 2016, *Journal of Hematology*, *5*(1), 38–40. https://doi.org/10.14740/jh266e
68 Treleaven, J. G., & Win, N., Hyperhaemolysis syndrome in a patient with myelofibrosis, 2004, *Hematology*, *9*(2), 147–149. https://doi.org/10.1080/1024533042000205478
69 Vagace, J. M., Casado, M. S., Bajo, R., & Gervasini, G., Hyperhaemolysis syndrome responsive to splenectomy in a patient with δβ-thalassaemia: A discussion on underlying mechanisms, 2014, *Blood Transfusion*, *12*(1), 127–129. https://doi.org/10.2450/2013.0059-13
70 Mechery, J., Abidogun, K., Crosfill, F., & Jip, J., Hyperhemolysis syndrome complicating pregnancy in homozygous δβ-thalassemia, 2012, *Hemoglobin*, *36*(2), 183–185. https://doi.org/10.3109/03630269.2011.649150
71 Bezirgiannidou, Z., Christoforidou A., Kontekaki, E., Anastasiadis, A.G, Papamichos, S.I., Menexidou, H., Margaritis,D., Martinis, G. and Mantadakis, E., Hyperhemolytic Syndrome Complicating a Delayed Hemolytic Transfusion Reaction due to anti-P1 Alloimmunization, in a Pregnant Woman with HbO-Arab/β-Thalassemia, *Mediterr J Hematol Infect Dis.* 2016; 8(1): e2016053.Published online 2016 Oct 18. doi: 10.4084/MJHID.2016.053

Figure 1: Overview of the progression over time of hemoglobin, LDH and erythroblasts



Legend: Hb: hemoglobin (a), LDH: Lactate dehydrogenase (b); erythroblasts (c); PRBC: packed red blood cells (bright dots); steroids (dark dots); IVIG: Intravenous immunoglobulin (bars). The days on the x-axis refer to the days before, during, and after hospitalization, the y- axis the units of the respective measured values.

Table 1: Overview of the phenotypes of the pRCBs administered

genotype patient:		*RHD*01*, *RHCE*02*, *RHCE*03*, *FY*01*, *FY*02*, *JK*01*, *JK*02*, *KEL*01.01*, *KEL*02*; GYPA*01, GYBB*04	
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-), 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+	unknown
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.

Table 2: Overview of the hemoglobin 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	

Table 3: Overview of published case reports related to a HHS

HHS Case Reports			
Authors	Title	Year	Published in
Aragona, E., & Kelly, M. J. [53]	Hyperhemolysis in sickle cell disease	2014	*Journal of Pediatric Hematology/Oncology*, *36*(1), 54–56. https://doi.org/10.1097/MPH.0b013e31828e529f
Chinchilla Langeber, S., Osuna Marco, M. P., Benedit, M., & Cervera Bravo, Á. [54]	When a transfusion in an emergency service is not really urgent: Hyperhaemolysis syndrome in a child with sickle cell disease	2018	*BMJ Case Reports*, *2018*. https://doi.org/10.1136/bcr-2017-223209
Cullis, J. O., Win, N., Dudley, J. M., & Kaye, T [37]	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. https://doi.org/10.1111/j.1423-0410.1995.tb00373.x
Eberly, L. A., Osman, D., & Collins, N. P. [55]	Hyperhemolysis Syndrome without Underlying Hematologic Disease	2015	*Case Reports in Hematology*, *2015*, 1–3. https://doi.org/10.1155/2015/180526
Epstein, S. S., & Hadley, T. J. [56]	Successful management of the potentially fatal hyperhaemolysis syndrome of sickle cell anaemia with a regimen including bortezomib and Hemopure	2019	*Journal of Clinical Pharmacy and Therapeutics*, *44*(5), 815–818. https://doi.org/10.1111/jcpt.12998
Fuja, C., Kothary, V., Carll, T. C., Singh, S., Mansfield, P., & Wool, G. D. [45]	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. https://doi.org/10.1111/trf.16932
Gouveia, M. E., Soares, N. B., Santoro, M. S. A., & de Azevedo, F. C. M. [57]	Hyperhemolysis syndrome in a patient with sickle cell anemia: Case report	2015	*Revista Brasileira de Hematologia e Hemoterapia*, *37*(4), 266–268. https://doi.org/10.1016/j.bjhh.2015.03.005
Gupta, S., Fenves, A., Nance, S. T.,	Hyperhemolysis syndrome in a patient	2015	*Transfusion*, *55*(3), 623–628. https://doi.org/10.1111/trf.12876

Sykes, D. B., & Dzik, W. [58]	without a hemoglobinopathy, unresponsive to treatment with eculizumab		
Kalter, J., Gupta, R., Greenberg, M., Miller, A., & Allen, J. [17]	Hyperhemolysis Syndrome in a Patient with Sickle Cell Disease: A Case Repor	2021	*Clinical Practice and Cases in Emergency Medicine*, *5*(1), 101–104. https://doi.org/10.5811/cpcem.2020.12.50349
Karatin, M. S., Singavi, A., Johnson, S. T., & Field, J. J. [59]	A fatal case of immune hyperhemolysis with bone marrow necrosis in a patient with sickle cell disease	2017	*Hematology Reports*, *9*(1), 8–11. https://doi.org/10.4081/hr.2017.6934
Kasinathan, G., & Sathar, J. [60]	Post-transfusion hyperhemolysis syndrome in a patient with beta thalassemia major	2021	*Clinical Case Reports*, *9*(6), 10–13. https://doi.org/10.1002/ccr3.4226
Lu, R. P., Clark, P., & Mintz, P. D. [61]	Hyperhemolysis sydrome: A relative contraindication for transfusion	2008	*Journal of Hospital Medicine*, *3*(1), 78–80. https://doi.org/10.1002/jhm.257
Menakuru, S. R., Priscu, A., Dhillon, V., & Salih, A. [44]	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	*Hematology Reports*, *14*(3), 235–239. https://doi.org/10.3390/hematolrep14030032
Narbey D, Habibi A, Chadebech P, Mekontso-Dessap A, Khellaf M; Lelièvre, JD, Godeau B, Michel M; Galactéros F, Djoudi R, Bartolucci P; Pirenne F [35]	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, R., Saadat, S. B., Tran, D. H., Constantinescu, S., & Qamruzzaman, Y. [62]	Recurrent Hyperhemolysis Syndrome in Sickle Cell Disease	2021	*Cureus*, *13*(5), 13–15. https://doi.org/10.7759/cureus.14991
Santos, B., Portugal, R., Nogueira, C., & Loureiro, M [63]	Hyperhemolysis syndrome in patients with sickle cell anemia: Report of three cases	2015	*Transfusion*, *55*(6), 1394–1398. https://doi.org/10.1111/trf.12993
Senanayake, M. P., Kuruppu, K. K., Sumanasena, S.	Hyperhaemolysis syndrome in haemoglobin E / beta	2008	*The Ceylon Medical Journal*, *53*(4), 134–135. https://doi.org/10.4038/cmj.v53i4.283

P., & Lamabadusuriya, S. P. [64]	thalassaemia responding to cyclophosphamide therapy		
Shankar, K., Shah, D., Huffman, D. L., Peterson, C., & Bhagavatula, R. [65]	Hyperhemolysis Syndrome in a Patient With Sickle Cell Disease and Acute Chest Syndrome	2021	*Cureus*, *13*(1), 1–5. https://doi.org/10.7759/cureus.13017
Sivapalaratnam, S., Linpower, L., Sirigireddy, B., Agapidou, A., Jain, S., Win, N., & Tsitsikas, D. A. [66]	Treatment of post-transfusion hyperhaemolysis syndrome in Sickle Cell Disease with the anti-IL6R humanised monoclonal antibody Tocilizumab	2019	*British Journal of Haematology*, *186*(6), e212–e214. https://doi.org/10.1111/bjh.16103
Sokolova, A., & Darabi, K [67]	A Case of Hyperhemolytic Anemia	2016	*Journal of Hematology*, *5*(1), 38–40. https://doi.org/10.14740/jh266e
Sweidan, A., Vuyyala, S., Xie, P., Alhyari, M., Dabak, V. S., & Otrock, Z. K. [10]	Hyperhemolysis Syndrome in SCD Patient: Reminder of a Rare but Life-Threatening Complication of Blood Transfusion	2021	*Blood*, *138*(Supplement 1), 4282–4282. https://doi.org/10.1182/blood-2021-152788
Treleaven, J. G., & Win, N. [68]	Hyperhaemolysis syndrome in a patient with myelofibrosis	2004	*Hematology*, *9*(2), 147–149. https://doi.org/10.1080/1024533042000205478
Uhlmann, E. J., Shenoy, S., & Goodnough, L. T. [28]	Successful treatment of recurrent hyperhemolysis syndrome with immunosuppression and plasma-to-red blood cell exchange transfusion	2014	*Transfusion*, *54*(2), 384–388. https://doi.org/10.1111/trf.12258
Vagace, J. M., Casado, M. S., Bajo, R., & Gervasini, G. [69]	Hyperhaemolysis syndrome responsive to splenectomy in a patient with δβ-thalassaemia: A discussion on underlying mechanisms	2014	*Blood Transfusion*, *12*(1), 127–129. https://doi.org/10.2450/2013.0059-13
Vlachaki, E., Gavriilaki, E., Kafantari, K., Adamidou, D., Tsitsikas, D., Chasapopoulou, E., Anagnostopoulos, A., & Tsapas, A. [41]	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. https://doi.org/10.1080/03630269.2018.1540353

Win, N., New, H., Lee, E., & De La Fuente, J. [18]	Hyperhemolysis syndrome in sickle cell disease: Case report (recurrent episode) and literature review	2008	*Transfusion*, *48*(6), 1231–1238. https://doi.org/10.1111/j.1537-2995.2008.01693.x

HHS Case Reports Related to Pregnancy

Authors	Title	Year	Published in	Treatment of HHS described
Asnawi, A. W. A., Sathar, J., Mohamed, R., Deraman, R., Kumaran, S., Hamid, S. S. A., & Zakaria, M. Z. [8]	Fatal Delayed Haemolytic Transfusion Reaction and Hyperhaemolysis Syndrome in a Pregnant Woman with Sickle Cell Anaemia	2016	*Indian Journal of Hematology and Blood Transfusion*, *32*(June), 251–253. https://doi.org/10.1007/s12288-014-0495-9	Blood exchange
Mechery, J., Abidogun, K., Crosfill, F., & Jip, J. [70]	Hyperhemolysis syndrome complicating pregnancy in homozygous δβ-thalassemia	2012	*Hemoglobin*, *36*(2), 183–185. https://doi.org/10.3109/03630269.2011.649150	Corticosteroids, IVIG, Cyclosporin
Vasanthamohan, L., Choo, S., Marshall, T., Symons, Y. T., Matsui, D., Eastabrook, G., & Solh, Z. [52]	Peripartum hyperhemolysis prophylaxis and management in sickle cell disease: A case report and narrative review	2020	*Transfusion*, *60*(10), 2448–2455. https://doi.org/10.1111/trf.16003	Prophylaxis: Corticosteroids, IVIG postpartum Rituximab
Wu, Y., Ji, Y., Dai, B., Guo, F., Wu, Y., He, Z., Mo, C., Wu, S., & Hu, Y. [9]	A case of hyperhaemolysis syndrome in a pregnant Chinese woman with β-thalassemia during perinatal transfusion	2021	*Transfusion Medicine*, *31*(1), 24–29. https://doi.org/10.1111/tme.12748	Corticosteroids, IVIG, Rituximab, Blood exchange
Bezirgiannidou, Z., Christoforidou A., Kontekaki, E., Anastasiadis, A.G, Papamichos, S.I., Menexidou, H., Margaritis,D., Martinis, G. and Mantadakis, E. [71]	Hyperhemolytic Syndrome Complicating a Delayed Hemolytic Transfusion Reaction due to anti-P1 Alloimmunization, in a Pregnant Woman with HbO-Arab/β-Thalassemia	2016	*Mediterr J Hematol Infect Dis.* 2016; 8(1): e2016053. Published online 2016 Oct 18. doi: 10.4084/MJHID.2016.053	Cortikosteroids, IVIG
Unnikrishnan, A., Pelletier, J.P.R., Bari, S., Zumberg, M., Shahmohamadi, A., Spiess, B.D., Michael, MJ., Harris, N., Harrell, D. and Mandernach, M.W. [26]	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	*The Journal of 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.