

Neue Therapieoptionen in der Behandlung der Hämophilie - Nicht-Faktor-basierte Therapie und Gentherapie

1. Larsson S. A. Life expectancy of Swedish haemophiliacs, 1831-1980. *British Journal of Haematology* 1985, 59, 593-602.
2. Oldenburg J, Dolan G, Lemm G. Haemophilia care then, now and in the future. *Haemophilia* 2009 Jan;15 Suppl 1:2-7.
3. Tagliaferri A. et al. Mortality and causes of death in Italian persons with haemophilia, 1990-2007. *Haemophilia* 2010, 1-10.
4. Plug I. et al. Mortality and causes of death in patients with hemophilia, 1992-2001: a prospective cohort study. *Journal of Thrombosis and Haemostasis* 2005, 4, 510-516.
5. Fischer K et al. RCTs and observational studies to determine the effect of prophylaxis in severe haemophilia. *Haemophilia* 2007, 13, 345-350.
6. Soucie, J. M. et al. Mortality among males with hemophilia: relations with source of medical care. The Hemophilia Surveillance System Project Investigators. *Blood* 2000, 96, 437-442.
7. Chorba T. L. et al. Effects of HIV infection on age and causes of death for persons with haemophilia A in the United States. *American Journal Haematology* 2001, 66, 229-240.
8. Brackmann, H.-H. Die Hemmkörper-Hämophilien. Risikofaktoren und Therapieoptionen. *Pharmazie unserer Zeit* 2005, 35, 58-64.
9. Lenting PJ, Denis CV, Christophe OD. Eficizumab, a bispecific antibody recognizing coagulation factors IX and X: how does it actually compare to factor VIII? *Blood* 2017 7;130(23):2463-2468.
10. Oldenburg J, Mahlangu JN, Kim B, Schmitt C, Callaghan MU, Young G, Santagostino E, Kruse-Jarres R, Negrier C, Kessler C, Valente N, Asikanius E, Levy GG, Windyga J, Shima M. Eficizumab Prophylaxis in Hemophilia A with Inhibitors. *N Engl J Med*. 2017 Aug 31;377(9):809-818.
11. Chowdary P. Inhibition of Tissue Factor Pathway Inhibitor (TFPI) as a Treatment for Haemophilia: Rationale with Focus on Concizumab. *Drugs*. 2018 Jun;78(9):881-890.
12. Pasi KJ, Rangarajan S, Georgiev P, Mant T, Creagh MD, Lissitchkov T, Bevan D, Austin S, Hay CR, Hegemann I, Kazmi R, Chowdary P, Gercheva-Kyuchukova L, Mamonov V, Timofeeva M, Soh CH, Garg P, Vaishnav A, Akinc A, Sørensen B, Ragni MV. Targeting of Antithrombin in Hemophilia A or B with RNAi Therapy. *N Engl J Med*. 2017 Aug 31;377(9):819-828.
13. Nathwani AC, Tuddenham EG, Rangarajan S, Rosales C, McIntosh J, Linch DC, Chowdary P, Riddell A, Pie AJ, Harrington C, O'Beirne J, Smith K, Pasi J, Glader B, Rustagi P, Ng CY, Kay MA, Zhou J, Spence Y, Morton CL, Allay J, Coleman J, Sleep S, Cunningham JM, Srivastava D, Basner-Tschakarjan E, Mingozzi F, High KA, Gray JT, Reiss UM, Nienhuis AW, Davidoff AM. Adenovirus-associated virus vector-mediated gene transfer in hemophilia B. *N Engl J Med*. 2011 Dec 22;365(25):2357-65.
14. Nathwani AC, Reiss UM, Tuddenham EG, Rosales C, Chowdary P, McIntosh J, Della Peruta M, Lheriteau E, Patel N, Raj D, Riddell A, Pie J, Rangarajan S, Bevan D, Recht M, Shen YM, Halka KG, Basner-Tschakarjan E, Mingozzi F, High KA, Allay J, Kay MA, Ng CY, Zhou J, Cancio M, Morton CL, Gray JT, Srivastava D, Nienhuis AW, Davidoff AM. Long-term safety and efficacy of factor IX gene therapy in hemophilia B. *N Engl J Med*. 2014 Nov 20;371(21):1994-2004.
15. Miesbach W, Meijer K, Coppens M, Kampmann P, Klamroth R, Schutgens R, Tangelder M, Castaman G, Schwäble J, Bonig H, Seifried E, Cattaneo F, Meyer C, Leebeek FWG. Gene therapy with adeno-associated virus vector 5-human factor IX in adults with hemophilia B. *Blood*. 2018 Mar 1;131(9):1022-1031.
16. George LA, Sullivan SK, Giermasz A, Rasko JEJ, Samelson-Jones BJ, Ducore J, Cuker A, Sullivan LM, Majumdar S, Teitel J, McGuinn CE, Ragni MV, Luk AY, Hui D, Wright JF, Chen Y, Liu Y, Wachtel K, Winters A, Tiefenbacher S, Arruda VR, van der Loo JCM, Zelenais O, Takefman D, Carr ME, Couto LB, Anguela XM, High KA. Hemophilia B Gene Therapy with a High-Specific-Activity Factor IX Variant. *N Engl J Med*. 2017 Dec 7;377(23):2215-2227.
17. Rangarajan S, Walsh L, Lester W, Perry D, Madan B, Laffan M, Yu H, Vettermann C, Pierce GF, Wong WY, Pasi KJ. AAV5-Factor VIII Gene Transfer in Severe Hemophilia A. *N Engl J Med*. 2017 Dec 28;377(26):2519-2530.

Inhibitoren des Komplementsystems: Erweiterung des therapeutischen Spektrums steht vor der Tür

1. Schmidt CQ, Lambris JD, Ricklin D. Protection of host cells by complement regulators. *Immunol.Rev.* 2016;274:152-171.
2. Hill A, Kelly RJ, Hillmen P. Thrombosis in paroxysmal nocturnal hemoglobinuria. *Blood* 2013;121:4985-4996.
3. Amara U, Rittirsch D, Flierl M et al. Interaction between the coagulation and complement system. *Adv.Exp.Med.Biol.* 2008;632:71-79.
4. Luzzatto L. Paroxysmal nocturnal hemoglobinuria: an acquired X-linked genetic disease with somatic-cell mosaicism. *Curr.Opin.Genet. Dev.* 2006;16:317-322.
5. Hernandez-Campo PM, Almeida J, Acevedo MJ et al. Detailed immunophenotypic characterization of different major and minor subsets of peripheral blood cells in patients with paroxysmal nocturnal hemoglobinuria. *Transfusion* 2008;48:1403-1414.
6. Richards SJ, Hillmen P. Immunophenotypic analysis of PNH cells. *Curr.Protoc.Cytom.* 2002;Chapter 6:Unit.
7. Nebe T, Schubert, J. et al. Flow cytometric analysis of GPI-deficient cells for the diagnosis of paroxysmal nocturnal hemoglobinuria (PNH). *J.Lab.Med.* 2003;27:257-265.
8. Hochsmann B, Rojewski M, Schrezenmeier H. Paroxysmal nocturnal hemoglobinuria (PNH): higher sensitivity and validity in diagnosis and serial monitoring by flow cytometric analysis of reticulocytes. *Ann.Hematol.* 2011;90:887-899.
9. Hillmen P, Lewis SM, Bessler M, Luzzatto L, Dacie JV. Natural history of paroxysmal nocturnal hemoglobinuria. *N.Engl.J.Med.* 1995;333:1253-1258.
10. de Latour RP, Mary JY, Salanoubat C et al. Paroxysmal nocturnal hemoglobinuria: natural history of disease subcategories. *Blood* 2008;112:3099-3106.
11. Socie G, Mary JY, De Gramont A et al. Paroxysmal nocturnal haemoglobinuria: long-term follow-up and prognostic factors. French Society of Haematology. *Lancet* 1996;348:573-577.
12. Brodsky RA, Young NS, Antonioli E et al. Multicenter phase 3 study of the complement inhibitor eculizumab for the treatment of patients with paroxysmal nocturnal hemoglobinuria. *Blood* 2008;111:1840-1847.
13. Hillmen P, Hall C, Marsh JC et al. Effect of eculizumab on hemolysis and transfusion requirements in patients with paroxysmal nocturnal hemoglobinuria. *N.Engl.J.Med.* 2004;350:552-559.
14. Hillmen P, Muus P, Dührsen U et al. Effect of the complement inhibitor eculizumab on thromboembolism in patients with paroxysmal nocturnal hemoglobinuria. *Blood* 2007;110:4123-4128.
15. Schubert J, Hillmen P, Röth A et al. Eculizumab, a terminal complement inhibitor, improves anaemia in patients with paroxysmal nocturnal haemoglobinuria. *Br.J.Haematol.* 2008
16. Hill A, Hillmen P, Richards SJ et al. Sustained response and long-term safety of eculizumab in paroxysmal nocturnal hemoglobinuria. *Blood* 2005;106:2559-2565.
17. Harder MJ, Kuhn N, Schrezenmeier H et al. Incomplete inhibition by eculizumab: mechanistic evidence for residual C5 activity during strong complement activation. *Blood* 2017;129:970-980.
18. Hochsmann B, Leichtle R, von Zabern I et al. Paroxysmal nocturnal haemoglobinuria treatment with eculizumab is associated with a positive direct antiglobulin test. *Vox Sang.* 2012;102:159-166.
19. Hill A, Rother RP, Arnold L et al. Eculizumab prevents intravascular hemolysis in patients with paroxysmal nocturnal hemoglobinuria and unmasks low-level extravascular hemolysis occurring through C3 opsonization. *Haematologica* 2010;95:567-573.
20. Risitano AM, Notaro R, Marando L et al. Complement fraction 3 binding on erythrocytes as additional mechanism of disease in paroxysmal nocturnal hemoglobinuria patients treated by eculizumab. *Blood* 2009;113:4094-4100.
21. Luzzatto L, Risitano AM, Notaro R. Paroxysmal nocturnal hemoglobinuria and eculizumab. *Haematologica* 2010;95:523-526.
22. Risitano AM, Notaro R, Luzzatto L et al. Paroxysmal nocturnal hemoglobinuria--hemolysis before and after eculizumab. *N.Engl.J.Med.* 2010;363:2270-2272.
23. Kristiansen M, Graversen JH, Jacobsen C et al. Identification of the haemoglobin scavenger receptor. *Nature* 2001;409:198-201.
24. Olson JS, Foley EW, Rogge C et al. NO scavenging and the hypertensive effect of hemoglobin-based blood substitutes. *Free Radic.Biol. Med.* 2004;36:685-697.

25. Schnog JJ, Jager EH, van der Dijs FP et al. Evidence for a metabolic shift of arginine metabolism in sickle cell disease. *Ann.Hematol.* 2004;83:371-375.
26. Hill A, Rother RP, Wang X et al. Effect of eculizumab on haemolysis-associated nitric oxide depletion, dyspnoea, and measures of pulmonary hypertension in patients with paroxysmal nocturnal haemoglobinuria. *Br.J.Haematol.* 2010;149:414-425.
27. Rother RP, Bell L, Hillmen P, Gladwin MT. The clinical sequelae of intravascular hemolysis and extracellular plasma hemoglobin: a novel mechanism of human disease. *JAMA* 2005;293:1653-1662.
28. Olsen SB, Tang DB, Jackson MR et al. Enhancement of platelet deposition by cross-linked hemoglobin in a rat carotid endarterectomy model. *Circulation* 1996;93:327-332.
29. Studt JD, Hovinga JA, Furlan M, Lammle B. Discrepant activity levels of von Willebrand factor-cleaving protease (ADAMTS-13) in congenital thrombotic thrombocytopenic purpura. *Blood* 2003;102:1148.
30. Schafer A, Wiesmann F, Neubauer S et al. Rapid regulation of platelet activation in vivo by nitric oxide. *Circulation* 2004;109:1819-1822.
31. Matejovic M, Krouzecky A, Radej J et al. Coagulation and endothelial dysfunction during longterm hyperdynamic porcine bacteremia--effects of selective inducible nitric oxide synthase inhibition. *Thromb.Haemost.* 2007;97:304-309.
32. Gralnick HR, Vail M, McKeown LP et al. Activated platelets in paroxysmal nocturnal haemoglobinuria. *Br.J.Haematol.* 1995;91:697-702.
33. Wiedmer T, Hall SE, Ortel TL et al. Complement-induced vesiculation and exposure of membrane prothrombinase sites in platelets of paroxysmal nocturnal hemoglobinuria. *Blood* 1993;82:1192-1196.
34. Hugel B, Socie G, Vu T et al. Elevated levels of circulating procoagulant microparticles in patients with paroxysmal nocturnal hemoglobinuria and aplastic anemia. *Blood* 1999;93:3451-3456.
35. Ploug M, Plesner T, Ronne E et al. The receptor for urokinase-type plasminogen activator is deficient on peripheral blood leukocytes in patients with paroxysmal nocturnal hemoglobinuria. *Blood* 1992;79:1447-1455.
36. Helley D, de Latour RP, Porcher R et al. Evaluation of hemostasis and endothelial function in patients with paroxysmal nocturnal hemoglobinuria receiving eculizumab. *Haematologica* 2010;95:574-581.
37. Grunewald M, Siegemund A, Grunewald A et al. Plasmatic coagulation and fibrinolytic system alterations in PNH: relation to clone size. *Blood Coagul.Fibrinolysis* 2003;14:685-695.
38. Kelly RJ, Hill A, Arnold LM et al. Long-term treatment with eculizumab in paroxysmal nocturnal hemoglobinuria: sustained efficacy and improved survival. *Blood* 2011;117:6786-6792.
39. Socie G, Schrezenmeier H, Muus P et al. Changing prognosis in paroxysmal nocturnal haemoglobinuria disease subcategories: an analysis of the International PNH Registry. *Intern.Med.J.* 2016;46:1044-1053.
40. Noris M, Remuzzi G. Atypical hemolytic-uremic syndrome. *N.Engl.J.Med.* 2009;361:1676-1687.
41. Nurnberger J, Philipp T, Witzke O et al. Eculizumab for atypical hemolytic-uremic syndrome. *N.Engl.J.Med.* 2009;360:542-544.
42. Kose O, Zimmerhackl LB, Jungraithmayr T, Mache C, Nurnberger J. New treatment options for atypical hemolytic uremic syndrome with the complement inhibitor eculizumab. *Semin.Thromb.Hemost.* 2010;36:669-672.
43. Legendre, C., Babu, S., Furman, R., and et al. Safety and efficacy of eculizumab in aHUS patients resistant to plasma therapy: Interim analysis from a Phase II trial. Abstract presented at the 43rd annual meeting of the American Society of Nephrology, Denver, CO, November 16-21, 2010. Available from: http://www.abstracts2view.com/asn/view.php?nu=ASN10L1_1338a&terms . 2011.
44. Muus, P., Legendre, C., Douglas, K., and et al. Safety and efficacy of eculizumab in aHUS patients on chronic plasma therapy: Interim analysis from a Phase II trial. Abstract presented at the 43rd annual meeting of the American Society of Nephrology, Denver, CO, November 16-21, 2010. Available from: http://www.abstracts2view.com/asn/view.php?nu=ASN10L1_157a&terms . 2011.
45. Licht C, Greenbaum LA, Muus P et al. Efficacy and safety of eculizumab in atypical hemolytic uremic syndrome from 2-year extensions of phase 2 studies. *Kidney Int.* 2015;87:1061-1073.
46. Howard JF, Jr., Utsugisawa K, Benatar M et al. Safety and efficacy of eculizumab in anti-acetylcholine receptor antibody-positive refractory generalised myasthenia gravis (REGAIN): a phase 3, randomised, double-blind, placebo-controlled, multicentre study. *Lancet Neurol.* 2017;16:976-986.

47. Biglarnia AR, Nilsson B, Nilsson T et al. Prompt reversal of a severe complement activation by eculizumab in a patient undergoing intentional ABO-incompatible pancreas and kidney transplantation. *Transpl.Int.* 2011;24:e61-e66.
48. West-Thielke P, Progar K, Campara M et al. Eculizumab for Prevention of Antibody-Mediated Rejection in Blood Group-Incompatible Renal Transplantation. *Transplant.Proc.* 2018;50:66-69.
49. Chandran S, Baxter-Lowe L, Olson JL, Tomlanovich SJ, Webber A. Eculizumab for the treatment of de novo thrombotic microangiopathy post simultaneous pancreas-kidney transplantation-a case report. *Transplant.Proc.* 2011;43:2097-2101.
50. Lanfranco L, Joly M, Del BA et al. Eculizumab for Thrombotic Microangiopathy Associated with Antibody-Mediated Rejection after ABO-Incompatible Kidney Transplantation. *Case.Rep.Transplant.* 2017;2017:3197042. doi: 10.1155/2017/3197042. Epub;2017 Dec 28.:3197042.
51. Roth A, Huttman A, Rother RP, Duhrsen U, Philipp T. Long-term efficacy of the complement inhibitor eculizumab in cold agglutinin disease. *Blood.* 2009;113:3885-3886.
52. Roth A, Duhrsen U. Cold agglutinin disease. *Eur.J.Haematol.* 2010;84:91.
53. Bommer M, Höchsmann B, Flegel W, Döhner H, Schrezenmeier H. Successful treatment of complement mediated refractory hemolysis associated with cold and warm autoantibodies using eculizumab. [abstract]. *Haematologica* 2011;94(suppl.2):241 abs. 0593.
54. Röth A, Bommer M, Hüttmann A et al. Complement Inhibition with Eculizumab in Patients with Cold Agglutinin Disease (CAD): Results from a Prospective Phase II Trial (DECADE Trial) [abstract]. *Blood* 2016;126:274.
55. Dumas G, Habibi A, Onimus T et al. Eculizumab salvage therapy for delayed hemolysis transfusion reaction in sickle cell disease patients. *Blood.* 2016;127:1062-1064.
56. Boonyasampant M, Weitz IC, Kay B et al. Life-threatening delayed hyperhemolytic transfusion reaction in a patient with sickle cell disease: effective treatment with eculizumab followed by rituximab. *Transfusion.* 2015;55:2398-2403.
57. Gupta S, Fenves A, Nance ST, Sykes DB, Dzik WS. Hyperhemolysis syndrome in a patient without a hemoglobinopathy, unresponsive to treatment with eculizumab. *Transfusion.* 2015;55:623-628.
58. Anliker M, Schmidt CQ, Harder MJ et al.: Complement activation by human anti-red cell antibodies: hemolytic potential of antibodies and efficacy of complement inhibitors assessed by a sensitive flow cytometric assay. *Transfusion* In press.
59. Sheridan D, Yu ZX, Zhang Y et al. Design and preclinical characterization of ALXN1210: A novel anti-C5 antibody with extended duration of action. *PLoS.ONE.* 2018;13:e0195909.
60. Lee JW, Rottinghaus ST, Lee LW et al. Results from a phase 3, multicenter, noninferiority study of ravalizumab (ALXN1210) versus eculizumab in adult patients with paroxysmal nocturnal hemoglobinuria (PNH) naive to complement inhibitors [abstract]. *EHA Learning Center* 2018;Jun 17, 2018; 218885:
61. Fukuzawa T, Sampei Z, Haraya K et al. Long lasting neutralization of C5 by SKY59, a novel recycling antibody, is a potential therapy for complement-mediated diseases. *Sci.Rep.* 2017;7:1080.
62. Nunn MA, Sharma A, Paesen GC et al. Complement inhibitor of C5 activation from the soft tick *Ornithodoros moubata*. *J.Immunol.* 2005;174:2084-2091.
63. Hill A, Wyndiga J, Robak T, Hellman J, Kulasekararaj A. RESULTS OF COBALT, A PHASE II CLINICAL TRIAL OF COVERSIN IN PNH [abstract]. *EHA Learning Center* 2018;Jun 15, 2018; 214790:
64. Ricardo A, Arata M, DeMarco S. Preclinical Evaluation of RA101495, a Potent Cyclic Peptide Inhibitor of C5 for the Treatment of Paroxysmal Nocturnal Hemoglobinuria [abstract]. *Blood* 2015;126:939.
65. Hill A, Schrezenmeier H, Hillmen P, Szer J, Pullon H. RA101495, a subcutaneously administered peptide inhibitor of complement component C5, for the treatment of paroxysmal nocturnal hemoglobinuria: phase 2 results [abstract]. *EHA Learning Center.* 2018;Jun. 15, 2018; 214782:
66. Hill A, Valls AG, Griffin M, Munir T, Borodovsky A. A Subcutaneously Administered Investigational RNAi Therapeutic (ALN-CC5) Targeting Complement C5 for Treatment of PNH and Complement-Mediated Diseases: Preliminary Phase 1/2 Study Results in Patients with PNH [abstract]. *Blood* 2016;128:3891:

67. Derhaschnig U, Gilbert J, Jager U et al. Combined integrated protocol/basket trial design for a first-in-human trial. *Orphanet.J.Rare.Dis.* 2016;11:134.
68. Jäger U, Gilbert JC, Panicker S. The anti C1s complement antibody TNT009 induces rapid complete remissions of anaemia in patients with primary cold agglutinin disease [abstract]. *EHA Learning Center* 2018;Jun 12, 2016; 135348:
69. Yuan X, Gavrilaki E, Thanassi JA et al. Small-molecule factor D inhibitors selectively block the alternative pathway of complement in paroxysmal nocturnal hemoglobinuria and atypical hemolytic uremic syndrome. *Haematologica* 2017;102:466-475.
70. Risitano AM, Notaro R, Pascariello C et al. The complement receptor 2/factor H fusion protein TT30 protects paroxysmal nocturnal hemoglobinuria erythrocytes from complement-mediated hemolysis and C3 fragment. *Blood* 2012;119:6307-6316.
71. Risitano ASM, Sahelijo L. Safety and Pharmacokinetics of the Complement Inhibitor TT30 in a Phase I Trial for Untreated PNH Patients [abstract]. *Blood* 2015;126:2137.
72. Sahu A, Kay BK, Lambris JD. Inhibition of human complement by a C3-binding peptide isolated from a phage-displayed random peptide library. *J.Immunol.* 1996;157:884-891.
73. Apellis Pharma. Apellis Pharmaceuticals Provides Update on Two Phase Ib Trials for Patients with Paroxysmal Nocturnal Hemoglobinuria (PNH). 2018. 1-7-2018.
<http://investors.apellis.com/news-releases/news-release-details/apellis-pharmaceuticals-provides-update-two-phase-ib-trials>
74. Benamu E, Montoya JG. Infections associated with the use of eculizumab: recommendations for prevention and prophylaxis. *Curr.Opin. Infect.Dis.* 2016;29:319-329.

Anti-D-Prophylaxe bei RhD-negativen Frauen

1. Gemeinsamer Bundesausschuss. Richtlinien des Gemeinsamen Bundesausschusses über die ärztliche Betreuung während der Schwangerschaft und nach der Entbindung („Mutterschafts-Richtlinien“). In der Fassung vom 10. Dezember 1985, veröffentlicht im Bundesanzeiger Nr. 60 a vom 27. März 1986 zuletzt geändert am 21. April 2016, veröffentlicht im Bundesanzeiger AT 19.07.2016 B5 in Kraft getreten am 20. Juli 2016. [online, Zugriff: 24.06.2018] URL: https://www.g-ba.de/downloads/62-492-1223/Mu-RL_2016-04-21_iK-2016-07-20.pdf
2. Richtlinie zur Gewinnung von Blut und Blutbestandteilen und zur Anwendung von Blutprodukten (Richtlinie Hämotherapie) aufgestellt gemäß §§12a und 18 Transfusionsgesetz von der Bundesärztekammer im Einvernehmen mit dem Paul-Ehrlich-Institut. Gesamtnovelle 2017. Deutscher Ärzteverlag GmbH Köln, 2017.
3. Statistisches Bundesamt. Bevölkerung nach Geschlecht und Staatsangehörigkeit, Stand 30.09.2017 [online, Zugriff: 24.06.2018] URL: https://www.destatis.de/DE/ZahlenFakten/GesellschaftStaat/Bevoelkerung/Bevoelkerungsstand/Tabellen/Zensus_Geschlecht_Staatsangehoerigkeit.html
4. Wagner FF, Kasulke D, Kerowgan M, Flegel WA. Frequencies of the blood groups ABO, Rhesus, D Category VI, Kell and of clinically relevant high-frequency antigens in South-Western Germany. *Infusionsther Transfusionsmed* 1995;22:285-90.
5. Wagner FF, Gassner C, Müller TH, et al. Molecular Basis of Weak D Phenotypes. *Blood* 1999;93:385-393.
6. Axt-Fliedner R, Wienzek-Lischka S, Sachs UJ, et al. Hämolytische Erkrankung des Fetus und Neugeborenen. Teil 1: Ätiologie, Pathogenese, Diagnostik und Therapie in der Schwangerschaft. *Transfusionsmedizin* 2018;8:95-110.
7. Flegel WA, Khull SR, Wagner FF. Primary anti-D immunization by weak D type 2 RBCs. *Transfusion* 2000;40:428.
8. Wagner T, Körmöcz GF, Buchta C et al. Anti-D immunization by DEL red blood cells *Transfusion* 2005;45:520-526.
9. Legler TJ: Fetale molekulargenetische Blutgruppenbestimmung aus mütterlichem Plasma. *Transfusionsmedizin* 2014;4:73-78
10. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. IQWiG-Berichte – Nr. 607: Nicht invasive Bestimmung des fetalen Rhesusfaktors zur Vermeidung einer mütterlichen Rhesussensibilisierung. Auftrag D16-01, Version 1.0, Stand 20.03.2018 [online, Zugriff: 24.06.2018]. URL: https://www.iqwig.de/download/D16-01_Bestimmung-fetaler-Rhesusfaktor_Abschlussbericht_V1-0.pdf
11. Behrens O, Lelle RJ. Die Rhesusprophylaxe – Geschichte und aktueller Stand. *Zentralbl Gynäkol* 1997;119:204-210.
12. Behrens O, Schneider J. Diagnostik und Therapie des M. haemolyticus fetalis. *Gynäkologe* 2000;33:812-827
13. Henseler O, Heiden M, Haschberger B, Hesse J, Seitz R. Bericht zur Meldung nach § 21 TFG für die Jahre 2010 und 2011. *Bundesgesundheitsbl* 2013;56:1352-1367
14. Rote Liste 2015. Rote Liste Service GmbH, Frankfurt/Main 2015
15. CSL Behring. Rhophylac 300 Fachinformation [online, Zugriff 24.06.2018]. URL: <http://www.cslobehring.de/docs/394/661/Rhophylac.pdf>
16. Octapharma GmbH. Gebrauchsinformation: Information für den Anwender, Rhesonativ. [online, Zugriff 24.06.2018] URL: http://www.octapharma.de/fileadmin/user_upload/octapharma.de/Produkte/Immunologie/Dokumente/GI_Rhesonativ_09.15.pdf
17. Slootweg YM, Kelewijn JM, de Kort WL et al. Facilitators and barriers for RhD-immunized women to become and remain anti-D donors. *Transfusion* 2018;58:960-968.
18. Kumpel B. Efficacy of RhD monoclonal antibodies in clinical trials as replacement therapy for prophylactic anti-D immunoglobulin: more questions than answers. *Vox Sanguinis* 2007;93:99-111.
19. Crowther C, Middleton P. Anti-D administration after childbirth for preventing Rhesus alloimmunisation. *Cochrane Database Syst Rev* 2000;(2):CD000021.
20. Lubusky M, Simetka O, Studnickova M. Fetomaternal hemorrhage in normal vaginal delivery and in delivery by cesarean section. *Transfusion* 2012;52:1977-1982.
21. De Haas M, Thurik FF, van der Ploeg CPB et al. Sensitivity of fetal RHD screening for safe guidance of targeted anti-D immunoglobulin prophylaxis: Prospective cohort study of a nation-wide programme in the Netherlands. *BMJ* 2016;355:i5789

22. Müller SP, Bartels I, Stein W, et al. The determination of the fetal RhD status from maternal plasma for decision making on Rh prophylaxis is feasible. *Transfusion* 2008;48:2292-301.
23. Axt-Fliedner R, Wienzek-Lischka S, Sachs UJ, et al. Hämolytische Erkrankung des Fetus und Neugeborenen. Teil 2: Diagnose und Therapie der hämolytischen Erkrankung des Neugeborenen, Primärprophylaxe. *Transfusionsmedizin* 2018;8:111-120.
24. Bowman JM: The prevention of Rh immunization. *Transf Med Rev* 1988;2:129-150
25. Statistisches Bundesamt. Die Statistik der Geburten Stand 2016 [online, Zugriff: 24.06.2018] URL: <https://www.destatis.de/DE/ZahlenFakten/GesellschaftStaat/Bevoelkerung/Geburten/Aktuell.html>
26. Ma KK, Rodriguez MI, Cheng. Should cell-free DNA testing be used to target antenatal rhesus immune globulin administration *J Matern Fetal Neonatal Med* 2016;29:1866-70
27. Clausen FB, Steffensen R, Christiansen M et al. Routine non-invasive prenatal screening for fetal RHD in plasma of RhD-negative pregnant women – 2 years of screening experience from Denmark. *Prenat Diagn* 2014;34:1000-1005
28. Haimila K, Sulin K, Kuosmanen M et al. Targeted antenatal anti-D prophylaxis program for RhD-negative pregnant women – outcome of the first two years of a national program in Finland. *Acta Obstet Gynecol Scand* 2017;96:1228-1233.
29. National Institute for Health and Care Excellence. High-throughput non-invasive prenatal testing for fetal RHD genotype. Stand 09.11.2016 [online, Zugriff: 24.06.2018]. URL: <https://www.nice.org.uk/guidance/dg25>
30. Minon JM, Gerard C, Senterre JM, et al. Routine fetal RHD genotyping with maternal plasma: a four-year experience in Belgium. *Transfusion* 2008;48:373-381
31. Wikman AT, Tiblad E, Karlsson A, et al. Noninvasive single-exon fetal RHD determination in a routine screening program in early pregnancy. *Obstet Gynecol* 2012;120:227-234.
32. Müller SP, Bartels I, Stein W, et al. Cell-free fetal DNA in specimen from pregnant women is stable up to 5 days. *Prenat Diagn* 2011;31:1300-4.
33. Clausen FB, Jakobsen TR, Rieneck K, et al. Pre-Analytical conditions in non-invasive prenatal testing of cell-free fetal RHD. *PLoS One*. 2013 Oct 18;8(10):e76990
34. Legler TJ, Liu Z, Mavrou A, et al. Workshop report on the extraction of fetal DNA from maternal plasma. *Prenatal Diagnosis* 2007;27:824-9.
35. Rouillac-Le Sciellour C, Serazin V, Brossard Y, et al. Noninvasive fetal RhD genotyping from maternal plasma. Use of a new developed free DNA fetal kit RhD. *Transfus Clin Biol* 2007;14:572–577
36. Benachi A, Delahaye S, Leticee N, Jouannic JM, Ville Y, Costa JM. Impact of non-invasive fetal RhD genotyping on management costs of rhesus-D negative patients: results of a French pilot study. *Eur J Obstet Gynecol Reprod Biol* 2012; 162: 28-32
37. Macher HC, Noguerol P, Medrano-Campillo P, et al. Standardization non-invasive fetal RHD and SRY determination into clinical routine using a new multiplex RT-PCR assay for fetal cell-free DNA in pregnant women plasma: results in clinical benefits and cost saving. *Clin Chim Acta* 2012; 413: 490-494
38. Teitelbaum L, Metcalfe A, Clarke G, et al. Costs and benefits of non-invasive fetal RhD determination. *Ultrasound Obstet Gynecol* 2015;45:84-8
39. Frohn C. Gezielte Rhesusprophylaxe – Spritze nur, wenn nötig. [online, Zugriff: 24.06.2018] URL: <https://ladr.de/rhesusprophylaxe>
40. Gemeinsamer Bundesausschuss. Beschluss des Gemeinsamen Bundesausschusses über die Einleitung des Beratungsverfahrens: Nichtinvasive Bestimmung des fetalen Rhesusfaktors zur Vermeidung einer mütterlichen Rhesus-Sensibilisierung im Rahmen der Vorsorgeuntersuchungen gemäß Mutterschafts-Richtlinien (Mu-RL). Stand 18.08.2016 [online, Zugriff: 24.06.2018] URL: https://www.g-ba.de/downloads/39-261-2691/2016-08-18_Einleitung-Beratungsverf_Rh-Prophylaxe.pdf

41. Pollack W, Ascari WQ, Crispen JF, et al. Studies on Rh Prophylaxis. II. Rh immune prophylaxis after transfusion with Rh-positive blood. *Transfusion* 1971;11:340-344
42. Querschnitts-Leitlinien zur Therapie mit Blutkomponenten und Plasmaderivaten. Bundesärztekammer auf Empfehlung ihres Wissenschaftlichen Beirats (Hrsg.). 4. überarbeitete Auflage. Deutscher Ärzteverlag GmbH Köln, 2009.
43. Ayache S, Herman JH. Prevention of D sensitization after mismatched transfusion of blood components: toward optimal use of RhIG. *Transfusion*. 2008;48:1990-1999
44. Transfusionsgesetz in der Fassung der Bekanntmachung vom 28. August 2007 (BGBl. I S. 2169), das zuletzt durch Artikel 3 des Gesetzes vom 18. Juli 2017 (BGBl. I S. 2757) geändert worden ist.

Leserfrage: EK-Temperatur bei Patienten mit dem Merkmal Anti-I

1. Roelcke, D.: Cold agglutination. Transfusion Medicine Review, 2 (1989) 140.
2. Die Bundesärztekammer im Einvernehmen mit dem Paul-Ehrlich-Institut: Richtlinie zur Gewinnung von Blut und Blutbestandteilen und zur Anwendung von Blutprodukten (Richtlinie Hämotherapie), Gesamtnovelle 2017.