**Group B meningococcal (MenB) vaccine failure (Bexsero®) with a penicillin-resistant strain in a young adult on long-term Eculizumab: Implications and important lessons for clinicians**

**Authors:**

Sydel R Parikh,1 Jay Lucidarme,2 Coralie Bingham,3 Paul Warwicker,4 Tim Goodship,5 Mary E Ramsay,1 Ray Borrow,2 Shamez N Ladhani.1,6

**Affiliations:**

1. Immunisation, Hepatitis and Blood Safety Department, Public Health England, London United Kingdom

2. Vaccine Evaluation Unit, Public Health England, Manchester United Kingdom

3. Exeter Kidney Unit, Royal Devon and Exeter Hospital, Devon United Kingdom

4. Lister Renal Unit, Lister Hospital, Hertfordshire United Kingdom

5. Institute of Human Genetics, Newcastle University, Newcastle United Kingdom

6. St. George’s University of London, London, United Kingdom

**Conflict of interest statements:** No authors declare competing interests.

**Funding:** none.

**Corresponding Author:**

Shamez N. Ladhani

Immunisation, Hepatitis and Blood Safety Department,

61 Colindale Avenue

Public Health England, London United Kingdom NW5 4DA

Tel: 020 8327 7155 Email: shamez.ladhani@phe.gov.uk

**Contributor’s Statements Page**

Sydel R Parikh and Shamez N Ladhani are responsible for national surveillance of meningococcal disease in England through the Immunisation Department at Public Health England; they drafted the initial manuscript

Ray Borrow and Jay Lucidarme are responsible for providing a national reference laboratory service for meningococcal disease through the meningococcal reference unit (MRU) at Public Health England; they carried out the molecular and genomic analysis of the meningococcal isolate, contributed to the discussion, and reviewed and revised the manuscript.

Coralie Bingham, Paul Warwicker, and Tim Goodship: are clinicians who manage patients with complex renal diseases, including those receiving complement inhibitors; they contributed to the discussion, and reviewed and revised the manuscript

All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

# Abstract

Eculizumab (Solaris®; Alexion) is a humanised monoclonal antibody that binds human complement C5 protein and inhibits the terminal complement pathway. It is currently recommended for the treatment of complement-mediated thrombotic microangiopathies. An unwanted complication of inhibiting complement, however, is an increased risk of invasive meningococcal disease (IMD). Here, we report the first case of meningococcal group B vaccine (4CMenB) failure in a young adult receiving eculizumab for atypical haemolytic uraemic syndrome. She developed IMD due to a vaccine-preventable and penicillin-resistant MenB strain four months after receiving two doses of 4CMenB whilst on long-term oral penicillin prophylaxis against meningococcal infection.

**Keywords:** atypical haemolytic uraemic syndrome, aHUS, eculizumab, invasive meningococcal disease, IMD, MenB disease, Bexsero®, penicillin-resistance, prevention

# Introduction

Monoclonal antibodies are increasingly used to treat a range of medical conditions. Eculizumab (Soliris®; Alexion) is a humanised monoclonal antibody that is a terminal complement inhibitor used to treat paroxysmal nocturnal haemoglobinuria (PNH),1 and atypical haemolytic uraemic syndrome (aHUS),2 although its use is extending to treat other immune-mediated conditions.3-5 In aHUS, defects of complement regulation leads to uncontrolled platelet, leukocyte, and endothelial-cell activation and thrombotic microangiopathy.2

Eculizumab binds with high affinity to human C5 complement and blocks the generation of complements C5a and C5b-9, thus preventing the formation of membrane attack complexes and pro-inflammatory activation, and preventing end-organ damage.1 An unwanted complication of complement inhibition, however, is an increased risk of infection with encapsulated bacteria, especially *Neisseria meningitidis.*6 Consequently, patients on Eculizumab are advised to receive meningococcal vaccination at least 14 days prior to initiating treatment.7

Until recently, licensed meningococcal vaccines only protected against four of the 12 meningococcal serogroups (A, C, W and Y). In Europe, serogroup B (MenB) is responsible for nearly all IMD cases.8 In 2013, a multi-component, protein-based, broad-spectrum meningococcal vaccine (4CMenB, Bexsero®, GSK) was licensed. Although licensed for protection against MenB, the vaccine antigens can be found on the surface of all meningococci and, therefore, offer protection regardless of capsular group. In the UK, the quadrivalent MenACWY conjugate vaccine and 4CMenB are recommended for at-risk individuals, including those receiving complement inhibitors.9 Here, we report the first case of 4CMenB vaccine failure in a fully-immunised young adult on penicillin prophylaxis who developed IMD caused by a vaccine-preventable and penicillin-resistant MenB strain during treatment with Eculizumab for aHUS.

# Case Description

A 22 year-old female presented to the Emergency Department with fever, myalgia, lethargy, sore throat and headache, but no rash, photophobia or neck stiffness. Six months previously, she was diagnosed with aHUS associated with the *CFH* mutation c.3643C>G; p.Arg1215Gly identified through genetic testing,10 after presenting with vomiting and diarrhoea, headache, oliguria, haemolytic anaemia, severe thrombocytopenia with bruising, acute renal injury requiring dialysis, and raised lactate dehydrogenase, consistent with a thrombotic microangiopathy (TMA). At the time, she was started on long-term Eculizumab and penicillin prophylaxis. She commenced treatment with Eculizumab 900mg on the day of presentation with aHUS and received 900 mg/week for four weeks, 1200mg one week later and a maintenance dose of 1200mg every two weeks. She also initially received ciprofloxacin chemoprophylaxis (500 mg twice daily) when she commenced Eculizumab, which was then changed to long-term low-dose penicillin (500mg twice daily). She had no other significant medical history.

Clinical examination was unremarkable. Her blood counts revealed elevated white cell (17·0 x 109/L) and neutrophil (15·8 x 109/L) counts, with normal renal and liver function. C-reactive protein was 5mg/L initially but increased to 150mg/L within 20 hours before falling gradually. Lumbar puncture revealed no evidence of meningitis. She was treated with IV ceftriaxone (2g twice daily) for seven days followed by 10 days of oral ciprofloxacin 500 mg twice daily. Gram-negative diplococci were identified in the blood culture after 24 hours. She was discharged within 24 hours and has remained well on oral penicillin prophylaxis.

**Vaccination history**

She had received the group C meningococcal conjugate vaccine as part of the national programme in 2000 and the quadrivalent ACWY meningococcal conjugate vaccine (MenACWY) with two doses of 4CMenB given one month apart when she was diagnosed with aHUS. Serum bactericidal antibody titres using rabbit complement (rSBA) two months after MenACWY vaccination were 1024, 8192, 1024 and 512 for serogroups A, C, W and Y, respectively. MenB SBA titres for patients on Eculizumab therapy are difficult to interpret because this assay utilises exogenous human complement which is inactivated by Eculizumab.

**Microbiology**

The national reference laboratory identified the meningococcal blood culture isolate as non-serogroupable, with a minimum inhibitory concentration (MIC) of 0·5 mg/L for penicillin, which was double the threshold (0·25 mg/L) for penicillin resistance. Genomic analysis identified the isolate as belonging to the ST-162 clonal complex, a strain with established pathogenic potential. The capsular gene *csb* (siaDb), however, was interrupted by IS*1301*-related sequence, making the isolate unlikely to cause disease in immunocompetent individuals. Its *penA* allele (*neis1753* allele 23) contained three mutations associated with reduced penicillin sensitivity (F504L, A510V, I515V). Within the PubMLST *Neisseria* database (pubmlst.org/Neisseria; accessed 08/12/15), this allele was predominantly associated with *N. gonorrhoeae* (82/1758 annotated genomes vs 2/5464 annotated meningococcal genomes). The allele was not observed among any annotated genomes for *N. lactamica* (n=127), *N. subflava* (n=20), *N. polysaccharea* (n=15), *N. mucosa* (n=14), or other *Neisseria* species. Comparison of the broader genomic region (*neis1740* to *neis1773*) with other cc162 genomes using the PubMLST genome comparator tool revealed an uncharacteristic region spanning from *neis1750* to *neis1756*. As with *neis1753*, the *neis1754*, *neis1755* and *neis1756* alleles were highly associated with *N. gonorrhoeae*, whilst *neis1750* and *neis1751* were novel variants. This suggested a recombination event in an ancestral strain involving DNA of putative gonococcal origin.

The isolate also possessed genes for PorA P1.22,14, factor H binding protein (fHbp) peptide 3.31, and Neisserial Heparin Binding Antigen (NHBA) peptide 20, but was Neisserial adhesion A(*nadA*) negative*.*Meningococcal Antigen Typing System (MATS) analysis confirmed the strain as vaccine-preventable because of NHBA positivity.

**DISCUSSION**

Our case highlights the difficulties in protecting patients on inhibitors of the terminal complement pathway against meningococcal disease, even with vaccination and antibiotic chemoprophylaxis. Individuals on long-term Eculizumab who are not otherwise immunosuppressed usually develop high serum bactericidal antibody titres after meningococcal vaccination. However, the critical functions of the terminal complement pathway and, therefore, the ability to attract pro-inflammatory cells and initiate cell destruction by triggering pore formation, are impaired (even though the proximal complement pathway remains intact). Inherited deficiencies of the terminal complement pathway are rare (0·03% of the general population), but associated with a 7,000-10,000-fold higher risk of IMD, with 50-60% experiencing ≥1 IMD episode.11 In those with C5 deficiency, meningococciare responsible for >95% of invasive infections, with meningitis being the most common presentation (77%), and 42% suffer recurrent disease, both in terms of relapse and newly-acquired infections.11 Recurrent infections occur despite an adequate antibody response against the infecting meningococci; *in vitro* studies have shown that these antibodies will kill the homologous isolate, but only when complement is added to the assay.12

Interestingly, individuals with complement deficiency often have mild disease with low case fatality.11 One possible explanation is a less intense inflammatory response to infection because of lower endotoxin release from the bacterial surface in the absence of an intact terminal complement pathway.11 We recently showed that Eculizumab inhibited complement-mediated serum bactericidal activity but did not impede opsonophagocytic activity in patients on long-term Eculizumab therapy.13 Opsonophagocytic activity is triggered by binding of C3 complement without requirement of the terminal complement and may, therefore, help protect against severe infection.

The increased risk of IMD in patients receiving Eculizumab is well-recognised,7 with clear recommendations for meningococcal vaccination of patients ≥2 weeks prior to commencing treatment,14 and many clinicians advocate life-long antibiotic chemoprophylaxis for added protection.15-17 In a recent evaluation of 195 patients on Eculizumab, two IMD cases were identified during 467 patient-years of Eculizumab exposure (0∙42 infections/100 patient-years).18 Both cases had received various meningococcal vaccines but developed IMD due to a non-vaccine serogroup. In another report, a 19 year-old with factor H mutation, three renal transplants and receiving several immunosuppressives and Eculizumab, developed MenW septicaemia.16 She had been immunised 18 months previously with a MenACWY polysaccharide vaccine, which is likely to be less protective than the equivalent conjugate vaccine.

Recently, a toddler with aHUS diagnosed in infancy and receiving long-term Eculizumab developed MenW septicaemia despite prior immunisation with the MenACWY conjugate vaccine.15 He was also on amoxicillin prophylaxis at the time and the responsible MenW strain had intermediate penicillin sensitivity, with a minimal inhibitory concentration of 0·13 mg/L (sensitive, 0·06 mg/L, resistant >0·25 mg/L). This child, too, had mild disease without complications. After her illness, she had non-protective antibody titres against serogroups C, W and Y, but responded with high antibody titres after a further dose of the MenACWY conjugate vaccine.

The recent licensure of 4CMenB was heralded as a major breakthrough because it aimed to provide universal protection against meningococcal disease. Our patient was immunised with the MenACWY conjugate vaccine and 4CMenB, and was on long-term penicillin prophylaxis when she developed MenB disease due to a penicillin-resistant and vaccine-preventable strain. Current guidelines recommend testing antibody responses in patients receiving Eculizumab before and 4-6 weeks after meningococcal vaccination, and subsequently every 1-3 years with a view to re-immunise if antibody titres are below protective thresholds.18,19 More data are needed to support this recommendation, given that these vaccine-induced antibodies require a functional terminal complement pathway to kill the meningococci efficiently. The development of IMD due to a penicillin-resistant strain in our patient and the published paediatric case is also concerning, given that penicillin resistance among meningococci is rare (<5%).

Our case highlights the importance of making patients with aHUS and their care givers aware of their increased risk of meningococcal disease and to seek medical attention early. Paediatricians are increasingly going to manage children and adolescents on long-term complement inhibitors20 and these age-groups also have the highest burden of meningococcal disease21 Manufacturers of Eculizumab supply an alert card, which patients are asked to carry at all times, to alert clinicians to their increased risk of IMD. Having a national service for aHUS allows adverse events to be monitored centrally, reported regularly and acted upon quickly through national and international recommendations.22,23 In the UK, the national support group (aHUSUK; [www.ahusuk.org](http://www.ahusuk.org)) plays a pivotal role in emphasising the on-going risk of IMD and the need for vigilance and immediate action (<http://ahusuk.org/important-to-remember/>).

# References

1. Hillmen P, Young NS, Schubert J, et al. The complement inhibitor eculizumab in paroxysmal nocturnal hemoglobinuria. *N Engl J Med* 2006; **355**(12): 1233-43.

2. Legendre CM, Licht C, Muus P, et al. Terminal complement inhibitor eculizumab in atypical hemolytic-uremic syndrome. *N Engl J Med* 2013; **368**(23): 2169-81.

3. Reis ES, Mastellos DC, Yancopoulou D, Risitano AM, Ricklin D, Lambris JD. Applying complement therapeutics to rare diseases. *Clin Immunol* 2015; **161**(2): 225-40.

4. Nester CM, Brophy PD. Eculizumab in the treatment of atypical haemolytic uraemic syndrome and other complement-mediated renal diseases. *Curr Opin Pediatr* 2013; **25**(2): 225-31.

5. Bomback AS. Eculizumab in the treatment of membranoproliferative glomerulonephritis. *Nephron Clin Pract* 2014; **128**(3-4): 270-6.

6. Nester CM, Thomas CP. Atypical hemolytic uremic syndrome: what is it, how is it diagnosed, and how is it treated? *Hematology Am Soc Hematol Educ Program* 2012; **2012**: 617-25.

7. Administration FaD. BLA 125166/172 SOLIRIS® (ECULIZUMAB) In: Inc. AP, editor.: Food and Drug Administration; 2014.

8. Harrison LH, Trotter CL, Ramsay ME. Global epidemiology of meningococcal disease. *Vaccine* 2009; **27 Suppl 2**: B51-63.

9. England PH. Meningococcal: the green book, chapter 22. Public Health England; 2015. p. 14-5.

10. Warwicker P, Goodship TH, Donne RL, et al. Genetic studies into inherited and sporadic hemolytic uremic syndrome. *Kidney Int* 1998; **53**(4): 836-44.

11. Figueroa JE, Densen P. Infectious diseases associated with complement deficiencies. *Clin Microbiol Rev* 1991; **4**(3): 359-95.

12. Figueroa J, Andreoni J, Densen P. Complement deficiency states and meningococcal disease. *Immunol Res* 1993; **12**(3): 295-311.

13. Findlow J, Bai X, Carr D, et al. Effect of the Eculizumab (Solaris), on the meningococcal serogroup B serum bactericidal antibody activity and opsonophagocytic activity. Congress of EMGM. Amsterdam; 2015.

14. Keating GM. Eculizumab: a review of its use in atypical haemolytic uraemic syndrome. *Drugs* 2013; **73**(18): 2053-66.

15. Cullinan N, Gorman KM, Riordan M, Waldron M, Goodship TH, Awan A. Case report: Benefits and challenges of long-term eculizumab in atypical hemolytic uremic syndrome. *Pediatrics* 2015; **135**(6): e1506-9.

16. Struijk GH, Bouts AH, Rijkers GT, Kuin EA, ten Berge IJ, Bemelman FJ. Meningococcal sepsis complicating eculizumab treatment despite prior vaccination. *Am J Transplant* 2013; **13**(3): 819-20.

17. Zlamy M, Hofer J, Elias J, et al. Immunogenicity of meningococcus C vaccination in a patient with atypical hemolytic uremic syndrome (aHUS) on eculizumab therapy. *Pediatr Transplant* 2012; **16**(6): E246-50.

18. Hillmen P, Muus P, Roth A, et al. Long-term safety and efficacy of sustained eculizumab treatment in patients with paroxysmal nocturnal haemoglobinuria. *Br J Haematol* 2013; **162**(1): 62-73.

19. Group aRD. Haemolytic Uraemic Syndrome (Atypical, aHUS) – Clinician Information. 05/01/2015 2015. <http://rarerenal.org/clinician-information/haemolytic-uraemic-syndrome-atypical-ahus-clinician-information/> (accessed 18/01/2016 2016).

20. Noris M, Caprioli J, Bresin E, et al. Relative role of genetic complement abnormalities in sporadic and familial aHUS and their impact on clinical phenotype. *Clin J Am Soc Nephrol* 2010; **5**(10): 1844-59.

21. Ladhani SN, Ramsay M, Borrow R, Riordan A, Watson JM, Pollard AJ. Enter B and W: two new meningococcal vaccine programmes launched. *Arch Dis Child* 2016; **101**(1): 91-5.

22. Loirat C, Fakhouri F, Ariceta G, et al. An international consensus approach to the management of atypical hemolytic uremic syndrome in children. *Pediatr Nephrol* 2016; **31**(1): 15-39.

23. Sheerin NS, Kavanagh D, Goodship TH, Johnson S. A national specialized service in England for atypical haemolytic uraemic syndrome-the first year's experience. *QJM* 2016; **109**(1): 27-33.